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Drinking Water Criteria Document for Aldicarb (Final Draft)

(U.S.) Environmental Protection Agency
Cincinnati, OH

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The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on aldicarb.
This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of aldicarb
- Toxicokinetics and human exposure to aldicarb
- Health Effects of aldicarb in humans and animals
- Mechanisms of toxicity of aldicarb
- Quantification of toxicological effects of aldicarb

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DRINKING WATER CRITERIA DOCUMENT FOR ALDICARB

Prepared for

OFFICE OF DRINKING WATER

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NOTICE

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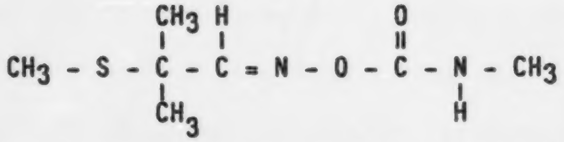
LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
ACh	Acetylcholine
AChE	Acetylcholinesterase
ADI	Acceptable daily intake
a.i.	Active ingredient
bw	Body weight
DNA	Deoxyribonucleic acid
ha	Hectare
HA	Health advisory
i.p.	Intraperitoneal
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse effect level
NAD	Nicotinamide-adenine dinucleotide
NADPH	Nicotinamide-adenine dinucleotide phosphate
NOAEL	No-observed-adverse effect level
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
RBC	Red blood cell
s.c.	Subcutaneous

I. SUMMARY

Aldicarb, 2-methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl)-oxime, is an oxime carbamate insecticide produced by the Union Carbide Corporation under the code number "UC 21149," trademark "Temik," and has the structural formula:



$$CH_3 - S - \overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}} - \overset{\overset{H}{|}}{C} = N - O - \overset{\overset{O}{\|}}{C} - \underset{\underset{H}{|}}{N} - CH_3$$

It is relatively soluble in water and most organic solvents. Aldicarb is a stable compound, except in strong alkaline solutions, and is nonflammable and noncorrosive to metal.

Aldicarb is a systemic pesticide used against a variety of insects and nematodes. The insecticide is applied below the soil surface for absorption by plant root systems, and moisture is required to release the toxicant from granules. Aldicarb is currently registered for use on a variety of crops including cotton, sugar beets, sugar cane, certain citrus fruits, potatoes, sweet potatoes, peanuts and ornamental plants; it may generally provide plant protection for a period of up to 12 weeks, depending on soil and climatic conditions. The half-life of aldicarb varies from ~1-2 weeks under laboratory conditions, but may be much shorter in the field or longer if it leaches to groundwater or if cool, nonalkaline conditions prevail.

A number of laboratory studies have demonstrated that aldicarb, as well as its sulfoxide and sulfone metabolites, is readily and almost completely absorbed through the gut in a variety of mammalian and nonmammalian species. Dermal absorption has been demonstrated in rabbits and rats, and might be expected to pose a problem to unprotected humans in manufacturing and field application settings. Studies examined in the preparation of this document indicate that aldicarb is widely distributed throughout the contaminated organism. However, since it is rapidly metabolized, its presence in individual tissues is generally transitory, given noncontinuous exposure.

The metabolism of aldicarb involves both hydrolysis of the carbamate ester and oxidation of the sulfur moeity to the sulfoxide and sulfone derivatives. While the hydrolysis results in compounds of little or no insecticidal activity or toxicity to other organisms, the sulfoxide and sulfone metabolites are active cholinesterase inhibitors. The metabolic degradation and elimination of aldicarb and its metabolites has been studied in a variety of species including rats, cows and chickens. In all studies to date, the primary means of aldicarb excretion has been found to be via the urine. Respiratory CO_2 and feces are other minor avenues through which this insecticide and its metabolites are eliminated from exposed animals. Aldicarb has been demonstrated to be rapidly excreted, with 80-90% being eliminated in the urine alone in a 24-hour period, depending on the individual species studied and the conditions of the experiment.

The acute toxicity of aldicarb has been studied in a variety of laboratory animals, including rats, mice, rabbits and chickens. Acute oral LD_{50} values ranged from 0.65-1.0 mg/kg bw in rats, with most studies producing LD_{50}s around 0.9 mg/kg. Mice were somewhat more susceptible to the acutely toxic effects of aldicarb, while chickens were the most tolerant. Dermal LD_{50} values for rats ranged from 2.5 mg/kg bw for females to 3.0 mg/kg bw for males. Rabbits were approximately twice as tolerant to dermal exposure to aldicarb as were the rats.

A number of chronic and subchronic feeding studies in mammals indicated the primary targets of aldicarb toxicity to be plasma, erythrocytes and the brain, with cholinesterase inhibition as the manifested effect. Long-term feeding studies in rats and dogs have produced NOELs ranging from 0.1 mg/kg bw/day to 0.3 mg/kg bw/day for aldicarb, aldicarb sulfoxide or a 1:1 sulfoxide:sulfone mixture. Aldicarb has been found to be noncarcinogenic, nonmutagenic and nonteratogenic in studies conducted to date, although one study did indicate a higher degree of cholinesterase inhibition measured in the livers of rat fetuses whose mothers had been exposed to aldicarb.

Human exposure, including accidental poisonings and a controlled laboratory study, have all produced symptoms which were cholinergic in nature and which all spontaneously subsided, generally within a 6-hour period. The range of symptoms observed in these cases have included malaise, blurred vision, arm and leg muscle weakness, epigastric cramping pain, excessive sweating, nausea, vomiting, nonreactive (to light) contracted pupils, dizziness, dyspnea, air hunger, diarrhea, muscle fasiculation and convulsions (in one case of accidental poisoning). The highest oral dosage producing no observable symptoms in the human study was 0.025 mg/kg, although the author indicated some degree of transient cholinesterase inhibition in subjects at this level also.

The primary mechanism of aldicarb toxicity is cholinesterase inhibition. Although it is commonly accepted that carbamate insecticides interfere with the ability of acetylcholinesterase (AChE) to break down the chemical transmitter acetylcholine (ACh) at synaptic and myoneural junctions, the precise biochemical mechanism for this interaction has yet to be clearly elucidated.

It is known, however, that the same mechanism of action is evident in both target and nontarget organisms. Aldicarb further causes depression of cholinesterases in the red blood cells and plasma of humans and other vertebrate organisms, but the degree of inhibition necessary to produce adverse effects in exposed organisms is the subject of current discussion.

The assessment criteria in this document are based upon studies of aldicarb sulfoxide and aldicarb sulfone, rather than the parent compound, itself. The use of these data, which provided the lowest NOELs of the chronic and subchronic studies, is considered valid, since aldicarb is very rapidly (and almost completely) metabolized to the sulfoxide, and subsequently to the less toxic sulfone, *in vivo*. Further, the sulfoxide metabolite and aldicarb have similar toxicities, and the effects of the parent compound are likely due to the presence of the sulfoxide (and, to a lesser extent, the sulfone).

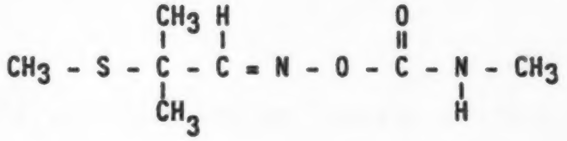
A thorough evaluation of the literature available to date confirms the 0.125 mg/kg/day NOEL from the Weil and Carpenter (1968b) 6-month rat feeding study as the most appropriate source of a NOEL for the determination of a human ADI. The Mirro et al. (1982) study of drinking water exposure in rats provides a supportive NOEL of 0.12, but suggests that a safety factor of 100 is in order since the NOEL is based upon consumption of a 1:1 ratio mixture of aldicarb sulfoxide and the less toxic sulfone. Although the Haines (1971) study provides the only data available involving controlled human experimentation, the single-dose treatment employed is not sufficiently comparable to the intermittent exposure associated with intake of a comparable level of toxicant over a prolonged period of time (i.e., 24-hour day or 16-hour waking day).

After due consideration of the available chronic and subchronic studies with aldicarb, aldicarb sulfoxide and aldicarb sulfone, the data from Weil and Carpenter (1968b) and Mirro et al. (1982) were considered the most suitable for the derivation of human ADI and HA criteria. Using the NOELs from the Weil and Carpenter (1968b) and Mirro et al. (1982) studies and applying a safety/uncertainty of 100, a human ADI of 1.2 μg/kg bw may be derived. Accordingly, 1-day and 10-day health advisories (HAs) of 42 μg/ℓ of water (84 μg total exposure) and 12 μg/ℓ of water (12 μg total exposure) may be calculated for a 70 kg adult and 10 kg child, respectively.

Since aldicarb is rapidly metabolized and excreted, the 1- and 10-day HA and AADI values would not be expected to differ to a significant or notable extent. The AADI, based upon the consumption of 2 ℓ water/day by a 70 kg adult, would therefore be 42 μg/ℓ. The AADI for a 10 kg child based upon the consumption of 1 ℓ water/day is 12 μg/ℓ. Since the 42 μg/ℓ AADI may not be sufficiently or adequately protective for a 10 kg child, and since such children comprise a substantial subset of the overall population, consideration should be given to establishing an AADI at 12 μg/ℓ, a level considered to be protective of the 10 kg child.

II. PHYSICAL AND CHEMICAL PROPERTIES

Aldicarb, 2-methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl)-oxime, is an oxime carbamate insecticide introduced in 1965 by the Union Carbide Corporation under the code number "UC 21149," tradename "Temik," and protected by U.S. patent no. 3,217,037 (Martin and Worthing, 1977). It is produced through the reaction of methyl isocyanate with 2-methyl-2-(methylthio)propanaldoxime (Payne et al., 1966), and is represented by the structural formula:



$$CH_3 - S - \overset{CH_3}{\underset{CH_3}{C}} - \overset{H}{C} = N - O - \overset{O}{\overset{\|}{C}} - \underset{H}{N} - CH_3$$

The physical and chemical properties of aldicarb, as specified in Kuhr and Dorough (1976) Martin and Worthing (1977) and/or FAO/WHO (1980) are as follows:

Properties, Characteristics and General Information:

Molecular weight:	190.3
Form:	white crystals (odorless to light sulfur smell)
Melting point:	100°C
Boiling point:	decomposes above 100°C
Vapor pressure:	0.05 torr @ 20°C
Specific gravity:	1.195 @ 25°C
Solubility:	in water -- 6 g/ℓ (room temperature) in heptane -- insoluble in most organic solvents -- soluble
Properties:	(1) stable (except to strong alkali) (2) noncorrosive to metal (3) nonflammable
CAS No.:	116-06-3
RTECS No.:	UE2275000

Synonyms listed by RTECS include:

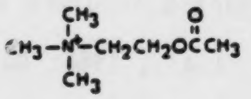
Aldecarb
Aldicarbe (French)
Carbamic acid, methyl-,
O-((2-Methyl-2-(methylthio)propylidene)amino) deriv.
Carbanolate
ENT 27,093
2-Methyl-2-(methylthio)propanal, O-((methylamino)carbonyl)oxime
2-Methyl-2-methylthio-propionaldehyd-O-(N-methyl-carbamoyl)-oxim (German)
2-Metil-2-tiometil-propionaldeid-O-(N-metil-carbamoil)-ossima (Italian)
NCI-C08640
OMS-771
Propanal, 2-methyl-2-(methylthio)-,
O-((methylamino)carbonyl))oxime
Temic
Temik G10
Temik 10 G
Union Carbide 21149
Union Carbide UC-21149

Aldicarb is a soil-applied systemic pesticide used against certain insects, mites and nematodes. It is applied below the soil surface for absorption by plant roots. To reduce its tendency to disperse in air as dusty particles capable of adhering to moist skin, aldicarb is commercially available only in the form of granules. One of the most widely used formulations of this pesticide (Temik) is available as Temik 10G and Temik 15G, which contain 10% and 15% aldicarb by dry weight, respectively. Aldicarb is therefore generally applied to the soil in the form of 10% or 15% granule and at application rates of 0.56-5.6 kg a.i./ha. Soil moisture is essential for the release of the toxicant from the granules, and uptake by plants is rapid. Duration of plant protection is generally up to 12 weeks (Martin and Worthing, 1977), although the actual duration of insecticidal activity may vary from 2-15 weeks, depending on the organism involved and the method of application (Hopkins and Taft, 1965; Cowan et al., 1966; Davis et al., 1966; Ridgway et al., 1966). The effective life of this insecticide will vary, however, depending on the type of soil, soil moisture and rainfall conditions, and the presence of soil microorganisms.

No production figures for aldicarb could be located in the available literature. However, total domestic consumption of this insecticide was reported to be 1.2 million pounds for commercial usage (SRI, 1984). (Home and garden use is not permitted.) No export figures were listed. This carbamate insecticide is currently registered for use on cotton, certain citrus fruits, sugar beets, sugar cane (Louisiana only), potatoes, sweet potatoes, peanuts, oranges, pecans (S.E. only), dry beans, soybeans and ornamental plants (Berg, 1981; CFR, 1982).

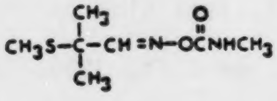
The environmental half-life of aldicarb has been reported to range from 1->54 days in soil, depending on soil type, moisture and temperature (Bull, 1968; Bull et al., 1970; Coppedge et al., 1967, 1977; Supak et al., 1977; U.S. EPA, 1975), with increased soil moisture and temperature resulting in shorter half-lives. The parent chemical is readily oxidized to form the more persistent, strongly basic and highly water-soluble sulfoxide which, in turn, is slowly oxidized to the sulfone. Hydrolysis reactions in the metabolic pathways of living organisms also degrade the aldicarb breakdown products to less toxic metabolites. The half-life of aldicarb is usually much shorter under field than laboratory conditions.

Structurally, the aldicarb molecule is similar to acetylcholine.



$CH_3-\overset{CH_3}{\underset{CH_3}{N^+}}-CH_2CH_2O\overset{O}{C}CH_3$

acetylcholine

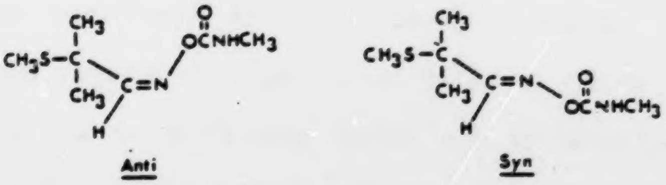


$CH_3S-\overset{CH_3}{\underset{CH_3}{C}}-CH=N-O\overset{O}{C}NHCH_3$

aldicarb

The mechanism of biological action of aldicarb is via cholinesterase inhibition (Kuhr and Dorough, 1976). Unlike the longer lasting anticholinesterase activity of the organophosphate pesticides, the carbamylation process which produces the anti-AChE action is more readily reversible (Goes et al., 1980). Takusagawa and Jacobson (1977) reported the molecular structure of the aldicarb crystal, as determined by single-crystal X-ray diffraction techniques, to consist of an orthorhombic unit cell with eight molecules per cell. The C-O single bond distance in the carbamate group was reported to be significantly longer than equivalent distances in carbolic acid esters, correlating positively with any theory of acetylcholinesterase activity involving disruption of this bond in a reaction with the AChE enzyme.

Aldicarb is known to have two geometrical isomers, as shown below.



Although it is not certain which isomer is the more active, evidence from the study of chemical degradation indicates the syn isomer is the one associated with the insecticide.

III. TOXICOKINETICS

Absorption

A number of studies have demonstrated that aldicarb, as well as its sulfoxide and sulfone metabolites, is absorbed readily and almost completely through the gut in a variety of mammalian and nonmammalian species (Knaak et al., 1966; Andrawes et al., 1967; Dorough and Ivie, 1968; Dorough et al., 1970; Hicks et al., 1972; Cambon et al., 1979). Dermal absorption has been demonstrated in rabbits (Kuhr and Dorough, 1976; Martin and Worthing, 1977) and rats (Gaines, 1969), and would be expected to present a problem to unprotected humans in manufacturing and field application settings. Although no information concerning dermal absorption of aldicarb in man could be located in the available literature, a study by Feldmann and Maibach (1970) demonstrated 73.9% absorption 5 days following application of carbaryl, another carbamate insecticide, to the human ventral forearm. While it would be highly speculative, at best, to suggest that this might be typically representative of the dermal absorption of all methylcarbamates, it should be noted that the extent of observed absorption in this study far exceeds the measured values of a number of organochlorine and organophosphate pesticides, which had absorption percentages ranging from 7.6-9.7% of the applied dose over the same period of time. In a separate, supporting study (Maibach et al., 1971), 69.9% of carbaryl applied to the human jaw angle and 73.9% applied to the forearm was reported to be excreted within 5 days of application. Data from this later study further demonstrate that dermal penetration of the organophosphate pesticides parathion and malathion is substantially dependent upon the particular anatomic area exposed.

Cambon et al. (1979) administered single doses of 0.001, 0.01 and 0.10 mg aldicarb (analytical grade 99%)/kg bw to pregnant Sprague-Dawley rats by gastric intubation on day 18 of pregnancy. Signs of poisoning occurred approximately 5 minutes after the administration of the larger doses, indicating the rapidity of absorption. At all dosage levels, AChE activity in the fetal blood, brain and liver was significantly decreased 1 hour after treatment.

The extent of gastrointestinal absorption of aldicarb has been noted in a number of studies. Andrawes et al. (1967) administered oral doses of radiolabeled aldicarb and aldicarb sulfoxide (as Temik and Temik Sulfoxide) to female rats and observed 80-90% excretion of the radiolabel in the urine and 2-5% in the feces within the first 24 hours following administration. Only trace amounts of Temik, per se, were found in the excreta, attesting to the degree of absorption. Knaak et al. (1966) further attested to the rapid and thorough absorption of aldicarb. Using oral administrations (weighed syringe technique) of Temik with radiolabels in three separate positions, these researchers reported that Temik was rapidly absorbed from the gastrointestinal tract. Further, by the end of the first 24 hours post administration, 90% of two of the labels had been excreted in urine or as CO_2 (this will be discussed further under "Excretion"), again indicating a high degree of absorption of the administered dose. When Dorough and Ivie (1968) fed rats milk containing radiolabeled Temik metabolites daily for 9 days, ~90% of each dose was reported to have been excreted in the urine within a 24-hour period.

Dorough et al. (1970) fed Holstein cows various levels of Temik in the diet and found that 1, 92 and 3% of the dosages were eliminated in the milk, urine and feces, respectively, indicating almost complete absorption of the administered dose through the gut. Dorough and Ivie (1968) administered a single dose (0.1 mg/kg bw) of radiolabeled Temik to a lactating Jersey cow and observed that over 96% of the radiolabel was eliminated from the body within 540 hours of treatment. The percentages of the dose eliminated were 3.0% in milk, 90.2% in the urine, and 2.9% in the feces.

Finally, Hicks et al. (1972) conducted a series of experiments in which White Leghorn laying hens were administered oral doses of radiolabeled aldicarb and aldicarb sulfone in both single dose and short-term feeding studies. These researchers found that 90% of the administered single doses of both chemicals had been excreted from the body within 10 days. In a 21-day study, they found that 90% of the total aldicarb administered had been eliminated within 1 week of cessation of administration.

All of these studies, although designed for other purposes, indicated rapid and/or reasonably complete uptake of aldicarb through the gut.

Distribution

Available studies indicate that aldicarb is widely distributed throughout the contaminated organism. However, since it is rapidly metabolized, invasion of individual tissues is generally temporary, given noncontinuous exposure.

In an experiment previously mentioned, Dorough et al. (1970) administered 0.12, 0.6 or 1.2 ppm Temik in the diet to Holstein cows for up to 14 days. Eighteen hours following the last radioactive Temik treatment, the animals were slaughtered and tissue samples removed for analysis. A total of 27 different tissue samples from each animal were examined for radiolabeled Temik equivalents. Twenty-two tissues from the cow fed 1.2 ppm Temik, 19 tissues from the cow receiving 0.6 ppm, and one tissue sample taken from the animal administered the lowest dosage level were found to contain detectable residues. In all animals, the liver contained the highest level of Temik equivalents. It is worthy of mention that, even at the highest dosage level, no residues could be detected in muscle, fat or bone tissue. A breakdown of the findings of this study are provided in Table III-1.

The carbamate pesticides, including aldicarb, or their active metabolites apparently reach tissues very quickly when given by the oral route (Cambon et al., 1979). Cambon et al. (1979, 1980) reported decreased activity in maternal and fetal cerebral AChE following administration of aldicarb to rats, indicating distribution to the fetus and invasion of brain tissue by aldicarb or its toxic metabolites. Cambon et al. (1979) further reported inhibition of AChE in other maternal and fetal tissues 1 hour following oral administration (by gastric intubation) of dosages as low as 0.001 mg aldicarb/kg bw.

Andrawes et al. (1967) administered oral doses of radiolabeled (sulfur-35) Temik to female rats at a level of 0.4 mg/kg. At designated times (5-11 days following treatment), two rats were killed and tissue

TABLE III-1

Radiolabeled Residues in Tissues of Cows Fed Temik-C^{14} for 14 Days[a,b]

Tissues[c]	ppb Temik equivalents at indicated feeding level[d]		
	Cow No. 1 (0.12 ppm)	Cow No. 2 (0.6 ppm)	Cow No. 3 (1.2 ppm)
Liver	29	123	164
Lungs	--	--	35
Kidney	--	6	16
Bile	--	9	16
Adrenal glands	--	6	12
Abomasum	--	4	11
Omasum	--	4	11
Large intestine	--	5	10
Ovaries	--	6	10
Rumen	--	5	10
Udder	--	6	10
Pancreas	--	5	9
Spinal cord	--	--	9
Gall bladder	--	4	8
Heart	--	6	8
Reticulum	--	6	8
Spleen	--	5	8
Skin	--	4	7
Small intestine	--	5	7
Brain	--	4	6
Neck muscle	--	--	6
Tongue	--	4	6

---

[a] Source: Dorough et al., 1970

[b] Animals slaughtered 18 hours after last treatment.

[c] Residues were not detected (below 4 ppb) in the following tissues: foreleg muscle, hindleg muscle, omental fat, subcutaneous fat, and rib bone.

[d] -- indicates residues below 4 ppb.

samples were removed and frozen for future analysis. Tissues analyzed included blood, heart, kidneys, brain, lungs, spleen, liver, leg muscle, fat, bone, stomach, small intestine and large intestine. Analysis of the tissue samples indicated a general distribution of radioactive residues, and there was no indication that any particular tissue or group of tissues was selective in sequestering aldicarb or its metabolites (Table III-2). Low levels of residues had been expected, since most of the administered dose had been excreted by the time the first animal was killed. Tissues taken from animals killed on the fifth day after treatment had no detectable radiolabeled residues.

Hicks et al. (1972) conducted a study in which the levels of residues of aldicarb and/or aldicarb sulfone in the eggs and tissues of chickens was determined. White Leghorn laying hens were administered (in gelatin capsules) either single oral doses of 0.7 mg radiolabeled aldicarb/kg bw, single doses of a 1:1 molar ratio of aldicarb-^{14}C and aldicarb sulfone-^{14}C, or 0.1, 1.0 or 20.0 ppm equivalent doses of the 1:1 molar ratio per day for 21 days. Both eggs and animal tissue samples were analyzed for the radiolabeled carbamate species. In eggs, it was found that adding aldicarb sulfone to the aldicarb resulted in higher levels of radiolabeled residues than when aldicarb alone was administered. Although the radioactive residues in the egg whites had declined by the third day post-treatment (single dose), the residues in the yolks were similar or showed a slight increase during the same period of time. As with the eggs, administering a combination of aldicarb and aldicarb sulfone seemed to result

TABLE III-2

Total ppm Temik Equivalents in Tissues of Rats Treated Orally with Sulfur-35 Temik at 0.4 mg/kg

Tissues	S-35 Temik equivalents at indicated days[b] (ppm)							
	1		2		3		4	
	W	D	W	D	W	D	W	D
Heart	0.12	0.44	0.09	0.32	0.08	0.29	0.11	0.38
Kidneys	0.16	0.56	0.08	0.25	0.06	0.16	0.07	0.21
Brain	0.11	0.35	0.02	0.08	0.08	0.25	0.05	0.19
Lungs	0.15	0.60	0.02	0.48	0.04	0.14	0.06	0.19
Spleen	0.27	1.08	0.04	0.12	0.10	0.37	0.05	0.17
Liver	0.16	0.28	0.07	0.22	0.07	0.21	0.05	0.14
Leg muscle	0.16	0.61	0.02	0.07	0.05	0.20	0.04	0.12
Fat	0.23	0.72	0.11	0.12	0.09	0.11	0.03	0.04
Bone	0.11	0.15	0.09	0.13	0.06	0.08	0.02	0.04
Stomach	0.19	0.64	0.07	0.26	0.08	0.29	0.06	0.19
Stomach contents	0.18	0.94	0.14	1.05	0.10	0.65	0.03	0.09
Small intestine	0.18	0.74	0.13	0.45	0.10	0.30	0.06	0.16
Small intestine contents	0.25	1.20	0.19	1.03	0.08	0.49	0.06	0.24
Large intestine	0.15	0.66	0.12	0.54	0.08	0.27	0.13	0.30
Large intestine contents	0.18	0.67	0.05	0.24	0.09	0.39	0.04	0.16
Blood	0.16	0.74	0.14	0.18	0.08	0.21	0.05	0.17

[a] Source: Andrawes et al., 1967

[b] W = wet weight; D = dry weight

in slightly higher tissue residues than did aldicarb alone. Residues in the tissues decreased sharply as the carbamates were eliminated from the body. Table III-3 shows the tissue distribution of the residue following single treatments with aldicarb by itself and with the 1:1 molar aldicarb-aldicarb sulfone mixture. In general, the quantity and nature of residues in the tissues of hens treated for 21 days with aldicarb and aldicarb sulfone were reasonably similar to those observed following the single treatments. Liver and kidney were found to contain the highest levels of residues.

Metabolism

Ryan (1971) provides a good general overview of the metabolism of carbamate insecticides. He reported that carbamates undergo a limited number of in vivo metabolic reactions, which may be classified as oxidation, reduction, hydrolysis and conjugation. Most of the enzymes involved in these processes are found in the microsomal fraction of liver homogenate, specifically in the subfraction from the smooth endoplasmic reticulum. The enzyme systems responsible for the oxidative metabolism of xenobiotics in general require oxygen and NADPH as cofactors. During the metabolic process, one atom of molecular oxygen is incorporated into the substrate through the action of monooxygenase enzymes. The mechanism apparently involves the reduction of a component of the microsomes by NADPH, which then reacts with molecular oxygen to form an "active oxygen" intermediate and transfers oxygen to the substrate. Cytochrome P-450 has been implicated as important in the activation of oxygen in the majority of the microsomal drug metabolizing enzymes.

The metabolism of aldicarb involves both hydrolysis of the carbamate ester and oxidation of the sulfur to the sulfoxide and sulfone derivatives

TABLE III-3

ppm Aldicarb Equivalents in Tissues and Eggs of Hens Treated with a Single Oral Dose of Aldicarb-S^{14} (A) or with an Equimolar Dose of Aldicarb-^{14}C and Aldicarb Sulfone-^{14}C (B)[a,b]

Tissue	ppm (wet wt.) Aldicarb-^{14}C equivalents after						
	6 hours		1 day		3 days		10 days[c]
	A	B	A	B	A	B	A
Kidney	0.59	0.73	0.19	0.21	0.09	0.11	0.020
Liver	0.53	0.68	0.26	0.31	0.10	0.14	0.034
Heart	0.28	0.35	0.12	0.09	0.07	0.05	0.010
Gizzard	0.26	0.31	0.11	0.08	0.04	0.06	0.020
Skin	0.22	0.25	0.08	0.08	0.04	0.05	0.004
Breast	0.20	0.32	0.08	0.08	0.03	0.05	0.006
Thigh	0.20	0.29	0.08	0.08	0.04	0.04	0.008
Leg	0.20	0.27	0.08	0.07	0.04	0.04	0.005
Blood	0.18	0.28	0.11	0.07	0.06	0.04	0.014
Brain	0.18	0.27	0.08	0.09	0.04	0.04	0.008
Fat	0.08	0.06	0.04	0.07	0.03	0.05	0.004
Egg yolk	d/	0.14	0.01	0.13	0.07	0.18	0.014
Egg white	d/	0.16	0.03	0.18	0.06	0.07	0.007

[a] Source: Hicks et al., 1972

[b] Dosage rate = 0.7 mg/kg

[c] Experiment involving treatment with B was terminated after 3 days

[d] No eggs laid

(Andrawes et al., 1967). While the hydrolysis results in compounds with little or no insecticidal activity or toxicity to other organisms, the sulfoxide and sulfone metabolites are active cholinesterase inhibitors (Andrawes et al., 1967; Bull et al., 1967; NAS, 1977). Figure III-1 shows the metabolic pathways of aldicarb in the rat suggested by Wilkinson et al. (1983). Aldicarb metabolites in animals include aldicarb sulfoxide, aldicarb sulfone, oxime sulfoxide, oxime sulfone, nitrile sulfoxide, nitrile sulfone, and at least five other metabolites (Knaak et al., 1966; Dorough et al., 1970). The variety of metabolites formed after incubation of aldicarb with rat liver microsomal enzymes is remarkably similar to those formed initially in the detoxification reactions in mammals, insects and plants (Oonnithan and Casida, 1967).

The rapid conversion of aldicarb to its sulfoxide and sulfone _in vivo_ has been reported to take place in both plants (Metcalf et al., 1966; Coppedge et al., 1967) and animals (Andrawes et al., 1967; Dorough and Ivie, 1968). Although a considerable amount of information concerning the metabolism of aldicarb in a variety of animal species is available, this section will deal with a few representative studies in this area. The metabolism of aldicarb by plants is discussed elsewhere in this document.

Knaak et al. (1966) studied the metabolic fate of the insecticide Temik labeled at three different positions (either S-methyl-C^{14}, tert-butyl-C^{14}, or N-methyl-C^{14}). In this experiment, male Carworth Farms-Elias stock rats were administered 50 μg oral doses (equivalent to 0.33 mg/kg bw) of radiolabeled Temik dissolved in polyethylene glycol 400 using the weighed syringe technique. Each labeled compound was administered to eight

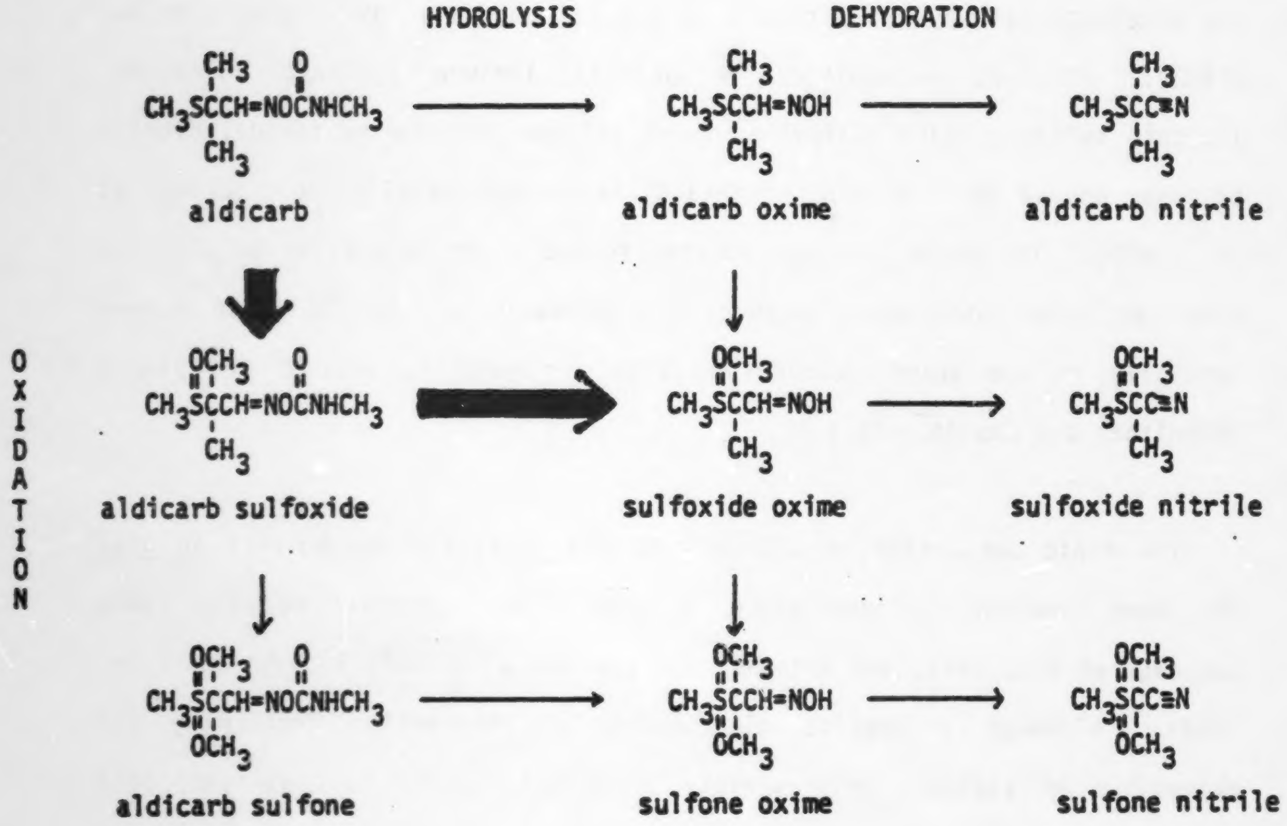

HYDROLYSIS
DEHYDRATION
OXIDATION
aldicarb
aldicarb oxime
aldicarb nitrile
aldicarb sulfoxide
sulfoxide oxime
sulfoxide nitrile
aldicarb sulfone
sulfone oxime
sulfone nitrile

FIGURE III-1

Metabolic Pathways of Aldicarb Metabolism in Rats

Source: Modified from Wilkinson et al., 1983 animals. In addition, groups of four rats per radiolabel were similarly administered 10 mg (66 mg/kg bw) of the S-methyl-C^{14} and t-butyl-C^{14} oxime analogues. The animals were maintained on a commercial synthetic diet to facilitate the collection of fecal material, and were housed individually in glass metabolism cages to permit the simultaneous collection of urine, feces and respired CO_2. Daily urine, fecal and CO_2 samples were taken from the test groups for a period of 4 days and analyzed; however, the daily urine and fecal samples from animals receiving N-methyl radiolabeled Temik were collected and analyzed over a period of 11 days. Results of this study indicated that Temik is metabolized in the rat and excreted in the first-day urine as Temik sulfoxide (~40%), oxime sulfoxide (~30%) and 5-9 other polar compounds (~30%) believed to be acids. Essentially all of the test compounds administered were metabolized by the rat. Only trace quantities of Temik (~1% as determined by gas chromatography) and of oxime and oxime sulfone (~1-2% as determined by silica gel chromatography) could be found in the urine. Evidence of Temik sulfone could not be found by either gas, silica gel or thin layer chromatography.

The metabolism of aldicarb has also been studied in a cow by Dorough and Ivie (1968). In this experiment, 40 mg of Temik-S^{35} (equivalent to a dose of 0.1 mg/kg bw) was administered orally in crushed grain to a lactating Jersey cow. Milk, urine and feces were then collected at 3, 6 and 12 hours post-treatment and at subsequent 12-hour intervals until no further radioactive residues could be detected. In a second part of this study, rats were fed daily doses of milk containing the radiolabeled Temik metabolites. The results of the study indicated that the metabolic pathway of Temik in dairy animals is similar to that reported for other animals. Temik sulfoxide and Temik sulfone are formed rapidly in the cow through oxidation of the sulfur atom but are quickly eliminated from the body, primarily in the urine. The Temik molecule and its oxidative metabolites further undergo hydrolysis to form a number of products that are eventually eliminated from the body. Although metabolism and elimination were initially rapid, there was a substantially slower release of those radioactive metabolites/residues remaining in the body after 48 hours. Metabolites detected in the milk were the same as those found in the urine. Metabolites found in the urine of both rats and cows included Temik sulfoxide, Temik sulfone, oxime sulfoxide, oxime sulfone, nitrile sulfoxide, nitrile sulfone, oxime, and a number of water-soluble and other unknown metabolites (Tables III-4 and III-5). In a follow-up study by Dorough et al. (1970), similar results were obtained when lactating Holstein cows were maintained on diets containing 0.12, 0.6 or 1.2 ppm radiolabeled Temik.

Knaak (1971), in a study of the metabolism of aldicarb in rats, suggested the following metabolic pathways:

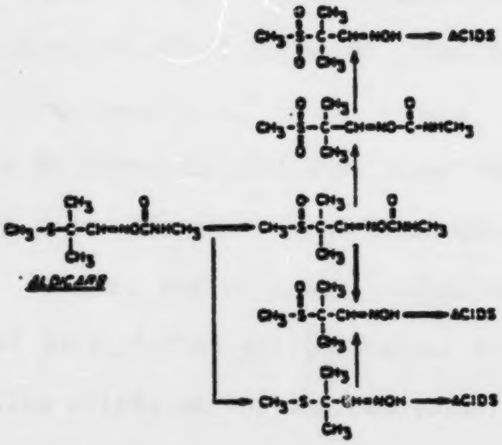


TABLE III-4

Organo-Extractable Urinary Metabolites from Cow Fed Temik-S^{35}[a,b]

Hours After Treatment	Percent of Total S^{35}-Organo-Extractables in Urine Present as Following Metabolites											
	UK-1	T-SO	UK-2	O-SO	UK-3	$T-SO_2$	N-SO	UK-4	UK-5	$O-SO_2$	$N-SO_2$	O
3	1.79	56.80	1.37	26.11	0.00	5.48	4.80	0.00	0.00	2.13	0.38	0.14
6	2.37	38.46	0.52	18.88	0.32	1.91	0.67	2.46	3.33	7.67	11.12	3.29
12	4.11	25.76	0	3.73	0.71	1.09	20.21	3.44	3.89	2.05	33.03	1.98
24	2.89	4.16	0	2.19	0.89	0.91	31.32	5.04	3.51	2.67	44.89	1.53
36	2.13	1.57	0	1.51	1.41	0	17.76	4.47	4.19	1.31	64.08	1.30
48	1.76	1.44	0	1.80	1.47	0	10.26	3.72	4.00	0.73	73.80	1.02
72	0.22	0.40	0	0.20	3.52	0	1.72	0	3.64	0	90.30	0
96	0	0	0	0	3.02	0	0.98	0	2.70	0	93.30	0
120	0	0	0	0	1.03	0	0.21	0	1.54	0	97.22	0
132	0	0	0	0	0.64	0	0	0	1.27	0	98.09	0
168	0	0	0	0	0	0	0	0	0.32	0	99.68	0
180-540	0	0	0	0	0	0	0	0	0	0	100.00	0

[a] Source: Dorough and Ivie, 1968

[b] UK: Metabolites of unknown identity

TABLE III-5

Metabolites Detected in Urine of Rats Fed milk from Cow Treated with Temik-S^{35}[a]

Metabolites	3-Hour Milk[b]	Percent of Total Radioactivity in Sample Present as Indicated Metabolite										
		Days										
		1	2	3	4	5	6	7	8	9[c]	10	11-14
Water-solubles	20.60[d]	56.75	53.46	54.81	51.29	54.44	53.77	52.20	50.55	53.26	52.62	51.98
Unknown 1	1.49	3.17	2.36	2.45	4.57	4.66	5.09	4.02	4.55	3.12	2.90	0
Temik sulfoxide	13.02	2.79	2.05	2.03	3.35	3.08	3.11	3.06	2.00	2.12	2.85	0
Unknown 2	0.53	1.57	1.85	1.37	0.95	1.13	1.25	1.08	1.26	1.74	0.93	0
Oxime sulfoxide	27.20	10.02	12.85	8.39	13.71	10.27	12.44	13.10	13.36	12.12	7.69	2.10
Unknown 3	1.52	0.69	0.71	0.84	0.61	0.78	1.22	0.72	0.53	0.77	0.61	0
Temik sulfone	4.82	0	0	0	0	0	0	0	0	0	0	0
Nitrile sulfoxide	22.48	9.55	9.30	9.44	8.69	8.45	7.51	8.42	8.64	10.80	8.42	6.70
Unknown 4	0.35	0	0	0	0	0	0	0	0	0	0	0
Unknown 5	0.67	0	0	0	0	0	0	0	0	0	0	0
Oxime sulfone	1.45	1.32	2.56	1.29	1.36	1.77	1.38	1.62	2.58	2.63	1.88	0
Nitrile sulfone	5.24	3.28	7.11	7.74	6.13	6.81	7.54	7.33	8.76	8.08	13.20	37.12
Oxime	0.63	6.10	5.33	7.65	6.81	5.79	4.31	5.01	4.78	3.35	5.11	2.10
Unknown 6	0	4.76	2.41	3.99	2.53	2.82	2.38	3.44	2.99	2.01	3.79	0

[a] Source: Dorough and Ivie, 1968

[b] Three-hour milk sample from cow treated with Temik-S^{35} that was used to feed rats for 9 days

[c] Last day rats received treatment

[d] Includes unextractable metabolites

Oonnithan and Casida (1967) studied the metabolism of 33 carbamate insecticides and related compounds by the rat liver microsome-reduced nicotinamide-adenine dinucleotide phosphate ($NADPH_2$) system. To determine whether or not the oxidation of Temik to the more toxic Temik sulfoxide was a function of microsomal enzymes, Temik was incubated with buffer alone, with buffer plus $NADPH_2$, and buffer plus microsomes, with and without $NADPH_2$ fortification. While Temik was found to be oxidised only partially to Temik sulfoxide in buffer alone, complete conversion to the sulfoxide derivative was observed in the buffer fortified with $NADPH_2$. Similarly, Temik incubated in the presence of a low concentration of microsomes without cofactor addition was found to oxidize completely to the sulfoxide and sulfone derivatives. However, Temik was reported to be metabolized almost completely without accumulation of ether-extractable, cholinesterase-inhibiting metabolites in the presence of microsomes plus $NADPH_2$ or when a high concentration of microsomes is used with or without $NADPH_2$ fortification. Upon incubation with microsomes alone, Temik sulfoxide was found to yield primarily the original compound, and fortification with $NADPH_2$ did not substantially increase the degradation of the sulfoxide. However, microsomes with or without $NADPH_2$ fortification were found to partially destroy the sulfone derivative without formation of ether-extractable cholinesterase inhibitors. The authors concluded that Temik does undergo sulfoxidation in a microsome-$NADPH_2$-catalyzed reaction, but the subsequent oxidation to the sulfone derivatives occurs only to a small extent.

In a similar experiment, Andrawes et al. (1967) investigated the metabolism of aldicarb (Temik) by a rat liver enzyme system. These researchers observed that very little metabolism of Temik occurred when the pesticide was incubated with various fractions of rat liver, unless the cofactor $NADPH_2$ was added. In the presence of $NADPH_2$, as much as a 15-fold increase in the overall metabolism of the compound was observed. These studies further indicated that the metabolism of Temik involved both hydrolysis of the carbamate ester and oxidation of the sulfur to Temik sulfoxide and Temik sulfone.

In a second part of the Andrawes et al. (1967) study, radiolabeled Temik and Temik sulfoxide were administered orally (unspecified dosage) in polyethylene glycol 400 (0.4 mℓ/animal) to adult female rats. Following dosing, the rats were housed individually in glass metabolism cages, where fecal and urine samples were collected at various intervals over a 24-hour period. Radioactive carbon dioxide evolution by carbonyl-^{14}C-treated rats was determined by continuously drawing air into the chamber and through two CO_2 absorption traps. The chemical nature of the Temik metabolites was determined through comparison of their chromatographic behavior and chemical properties with those of known standards. Temik metabolites recovered in the urine consisted of a combination of carbamate and hydrolytic products, the latter being predominant. Metabolites found in the urine included Temik oxime, Temik sulfoxide, Temik sulfone, oxime sulfoxide, oxime sulfone (all of which had also been identified in the previous liver microsome study), and two other chloroform-extractable materials considered to be hydrolytic products, since the carbonyl carbon was absent. The metabolite present in the greatest concentration was Temik sulfoxide (same as in the liver enzyme studies), which accounted for ~20% of the administered dose. The hydrolysis of Temik by the rats was further evidenced by the evolution of radioactive

CO_2, which alone indicated that more than 50% had been hydrolyzed within 8 hours of treatment and 61% by the end of a 24-hour period.

Hajjar and Hodgson (1982) studied the role of FAD-dependent monooxygenase from pig liver enzymes in the oxidation of sulfur- and phosphorus-containing pesticides. In this experiment, thioether-containing carbamates were generally found to be good substrates for the monooxygenase, although the rates of metabolism varied considerably depending on the particular substrate. Aldicarb was found to be metabolized at a rate of 1.15±0.12 nmoles NADPH·min^{-1}·(nmole enzyme)$^{-1}$. All of the carbamate substrates studied by the authors were metabolized primarily by oxidative attacks on the sulfur atoms, resulting in formation of the corresponding sulfoxide. It was further found that elimination of NADPH from the reaction medium resulted in quantitative recovery of the substrate. Hajjar and Hodgson (1982) concluded that, under aerobic conditions and in the presence of NADPH, the FAD-dependent monooxygenase from pig hepatic microsomes was responsible for the observed oxidation of thioether-containing carbamate pesticides. The authors further noted that (although not tested specifically on aldicarb) sulfoxidation was not inhibited, and in fact was enhanced, by n-octylamine, a known inhibitor of cytochrome P-450-dependent oxygenation.

Hicks et al. (1972) studied the metabolism of aldicarb in white Leghorn laying hens. In a series of three tests, birds were given either single 0.7 mg/kg bw oral doses (in a five grain gelatin capsule) of aldicarb-S^{35}, single oral doses of a 1:1 molar ratio of aldicarb-^{14}C and aldicarb sulfone-^{14}C (0.7 mg aldicarb equivalents/kg bw) in gelatin capsules, or 1:1 molar ratio doses of aldicarb-^{14}C and aldicarb sulfone-^{14}C at 0.1, 1.0 and 20.0 ppm diet every 12 hours for 21 days. In the latter test, nonradiolabeled insecticides were administered to the hens for 7 days prior to the radioactive feeding. Eggs and fecal samples were collected daily just prior to each of the insecticide administrations. Whether administered as a single dose or over an extended period of time, approximately half of the radioactive aldicarb residues in the feces consisted of unknown water soluble metabolites, which were formed very rapidly in the chickens. Of the identified metabolites, only aldicarb sulfoxide was found following a single dose, but not after repeated treatment. The authors stated that it was apparent that the sulfoxide derivative was formed and rapidly excreted. Aldicarb sulfone, similarly, was present in higher quantities in fecal samples taken 6 hours after administration of a single oral dose than in hens used in the continuous feeding study. Tables III-6 and III-7 list the metabolites recovered in the single and multiple feeding studies, respectively.

Excretion

The breadkdown and elimination of aldicarb and its metabolites has been studied in a variety of species including rats (Knaak et al., 1966; Andrawes et al., 1967; Dorough and Ivie, 1968; Marshall and Dorough, 1979), cows (Dorough and Ivie, 1968; Dorough et al., 1970), and chickens (Hicks et al., 1972). In all studies to date, the primary means of aldicarb excretion has been found to be via the urine. Exhaled CO_2 and feces are other avenues through which this insecticide and its metabolites are eliminated from exposed animals.

Knaak et al. (1966), in a study described in detail in the metabolism section of this chapter, reported that Temik was rapidly absorbed from

TABLE III-6

Nature of Radioactivity in Feces of Hens Treated with a Single Oral Dose of Aldicarb-S^{35} (A) or an Equimolar Dose of Aldicarb-^{14}C and Sulfone-^{14}C (B)[a,b]

Metabolites	Percent of Total Radioactivity in Sample After					
	6 hours		1 day		2 days	
	A	B	A	B	A	B
Aldicarb sulfoxide	5.1	13.3	0.0	0.6	0.0	0.0
Aldicarb sulfone	3.9	1.1	0	0	0	0
Aldicarb-NCH_2OH sulfone	1.0	1.6	0.9	5.8	2.7	5.5
Oxime sulfoxide	5.2	2.6	1.8	2.5	4.5	4.5
Oxime sulfone	2.8	14.6	4.1	10.6	5.6	9.9
Nitrile sulfoxide	2.3	4.2	2.3	1.3	2.4	2.9
Nitrile sulfone	7.2	4.2	9.2	5.4	16.3	10.7
Alcohol sulfoxide	1.8	1.4	2.0	1.2	5.9	2.8
Alcohol sulfone	1.7	1.6	1.7	3.0	7.7	4.9
Unknown 4	1.3	0.3	1.2	0	3.8	1.6
Unknown 5	5.9	1.9	3.3	2.0	0	0.9
Water-solubles	50.0	44.0	65.1	57.5	44.6	45.1
Unextractables	11.8	9.2	8.4	10.1	6.5	11.2
Cumulative percent of dose excreted[c]	50.2	48.0	74.3	76.1	84.5	79.3

[a] Source: Hicks et al., 1972

[b] Dosage rate = 0.7 mg/kg

[c] Values on day experiments terminated: A = 90% after 10 days, B = 82% after 3 days

TABLE III-7

Radioactive Residues in Feces of Hens Fed Equimolar Concentrations of Aldicarb-^{14}C and Aldicarb Sulfone-^{14}C in the Diet for 21 Days[a]

Metabolites	Percent of Total Radioactivity in Feces at Indicated Feeding Levels[b]		
	0.1 ppm	1.0 ppm	20.0 ppm
Aldicarb sulfone	0.0	0.6	0.9
Aldicarb-NCH_2OH sulfone	9.1	8.1	8.7
Oxime sulfoxide	0.0	1.7	0.8
Oxime sulfone	4.3	8.4	4.9
Nitrile sulfoxide	0.0	1.5	1.0
Nitrile sulfone	10.7	12.0	9.6
Alcohol sulfoxide	5.1	2.4	3.8
Alcohol sulfone	8.2	9.6	11.5
Unknown 4	0.0	0.6	1.4
Unknown 5	5.8	3.7	4.9
Water-solubles	48.1	43.8	43.3
Unextractables	8.7	7.6	9.2

[a] Source: Hicks et al., 1972

[b] Values are averages of analysis of feces collected 1, 2, 4, 12, 17 and 21 days after initiating feeding of the radioactive insecticides.

the gastrointestinal tract of rats and excreted in the urine and CO_2. Temik was observed to be metabolized and excreted in the first-day urine as Temik sulfoxide (40%), oxime sulfoxide (30%), and 5-9 other polar compounds believed to be acids (30%). Trace quantities of Temik (~1%) and oxime and oxime sulfone (1-2%) were detected by gas chromatography and silica gel chromatography, respectively; however, these latter results were stated to require further substantiating evidence before the presence of these metabolites in urine could be considered conclusive. The presence of Temik sulfone could not be detected by gas, silica gel or thin layer chromatography.

Knaak et al. (1966) further reported that the excretion of the S-methyl and tert-butyl labels from the radiolabeled Temik was 90% complete in 24 hours, while elimination of the N-methyl label was only 60% complete within the same period of time. By the fourth day post-treatment, 95.2% of the S-methyl-C^{14} radiolabel and 96.0% of the t-butyl-C^{14} radiolabel had been excreted (all routes considered). Urine accounted for the excretion of over 90% of the label in both cases, while CO_2 contained only 1.1% of the S-methyl-C^{14} label and 0.5% of the t-butyl-C^{14} label after 4 days. The N-methyl-C^{14} label was excreted much slower, with only ~70% having been excreted (all routes considered) in 4 days and 71.8% in an 11-day period. As opposed to the other two labels, however, CO_2 excretion accounted for a larger percentage (~25%) of the total radiolabel recovered after 4 days, as opposed to ~42% for urine. Fecal elimination was similar for all three radiolabels. Figure III-2 shows the 4-day results of both the Temik and oxime studies.

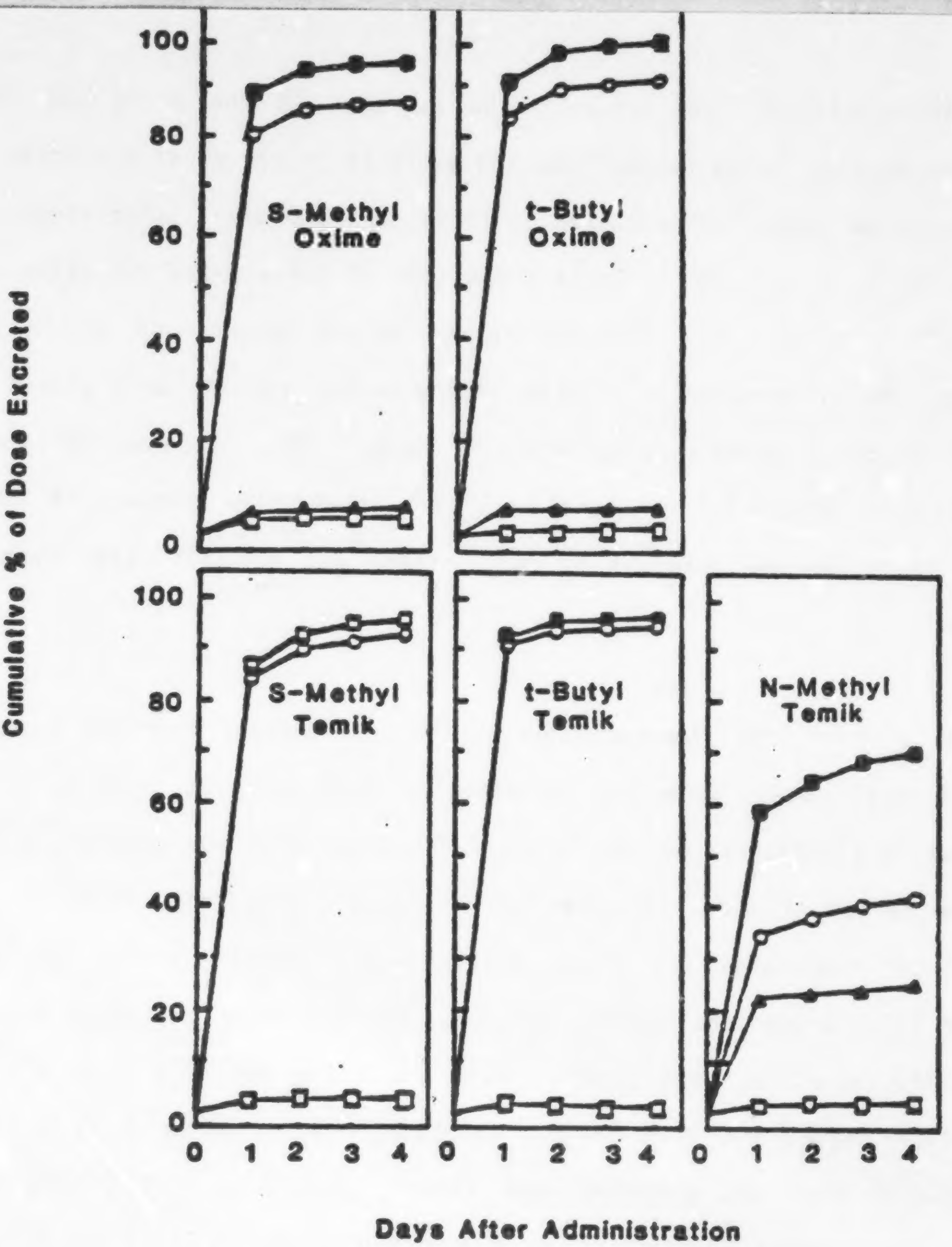


FIGURE III-2

Excretion of Temik-C^{14} and 2-methyl-2-(methylthio)propionaldehyde oxime-C^{14} by the rat[a,b]

[a] Source: Knaak et al., 1966

[b] C^{14} dose equivalents in: "□" - urine, feces and CO_2; "o" - urine; "Δ" - CO_2; "□" - feces. Male rats (150 g) were orally administered 50 µg of Temik (8 animals per label) and 10 mg of oxime (4 animals per label)

In a study previously described in the Metabolism section of this chapter, Andrawes et al. (1967) also studied the excretion of radiolabeled Temik. Adult female rats were administered oral 0.4 mℓ doses of radiolabeled Temik (equivalent to 0.4 mg/kg bw) or Temik sulfoxide (0.1 mg/kg bw), and urine, fecal and CO_2 elimination were measured over a 24-hour period. Four separate preparations of radioactive Temik (carbonyl-C^{14}, sulfur-35, S-methyl-C^{14} and tert-butylC^{14}) and two of Temik sulfoxide (sulfur-35 and carbonyl-C^{14}) were used. Urine and fecal samples were collected from each separately-housed animal at various intervals following dosing. Table III-8 shows the results of this study. With the exception of the rats treated with the carbonyl-C^{14} radiolabeled Temik, the administered label was excreted primarily in the urine. In the animals treated with the S-35, S-methyl-C^{14} and t-butyl-C^{14} preparations, an amount $\geq$50% of the applied label was accounted for in the urine within 12 hours. Although there was considerable variation in the total residues in the urine of the different groups at various sampling times, the cumulative radiolabel excreted during the first 24-hour period was reported to be almost identical (80% of the applied dose). The fecal samples from the treated animals accounted for only a very small portion of the administered dosage, with average total residues being only 1.4% of the dose in 24 hours. The Temik sulfoxide was similarly eliminated in the urine, feces and CO_2; however, the relative contributions of the various routes were different. By 24 hours after treatment, 36% of the carbonyl-C^{14} radiolabel was eliminated as CO_2, 47% in the urine and only 1.5% in the feces. By comparison, 75% of the S-35 Temik sulfoxide label had been recovered in the urine and 1.3% in the feces within the first 24 hours following treatment. In both sulfoxide treatment groups, over 95% of the radiolabel had been eliminated from

TABLE III-8

Excretion of Radioactivity in the Urine from Rats Treated Orally with Temik Labeled at Different Sites on the Molecule and Evolution of CO_2 from Rats Treated with Carbonyl-C^{14} Temik[a,b]

Hours After Treatment	Cumulative % of Dose Following Treatment with:				
	Carbonyl-C^{14} Temik	Carbonyl-C^{14} Temik	Sulfur-35 Temik	S-methyl-C^{14} Temik	Tert-butyl-C^{14} Temik
	CO_2-C-14	Urine			
2	19.81	11.26	10.96	16.03	26.42
4	38.06	21.25	10.96	16.03	38.56
8	57.38	24.17	34.79	47.56	60.31
12	59.74	27.10	48.29	59.05	67.48
16	60.74	28.68	55.35	67.68	73.13
20	61.16	29.27	67.47	67.68	75.50
24	61.54	29.40	79.17	78.91	77.24

[a] Source: Andrawes et al., 1967

[b] Temik administered at 0.4 mg/kg in polyethylene glycol

the body by the fourth day after administration of the sulfoxide (Table III-9).

In a separate study, Andrawes et al. (1967) administered 0.4 mg/kg bw doses of sulfur-35 Temik to determine the time necessary for a rat to be completely free of Temik residues. In this experiment, 12 female rats were administered the aldicarb treatment, and urine, fecal and certain tissue samples were assayed over a 24-day period. Table III-10 shows the pattern of excretion over the 24-day test period. From the results of this study, it was apparent that the substantial majority of the administered Temik was eliminated from the body within 2 days. The radiolabel remaining in the tissues was then slowly eliminated. The feces were found not to contain any detectable residues after the fourth day; however, 24 days were required for the urine to be free of all radiolabel. A total of 98.25% of the labeled dose was eliminated from the body by these two routes during the 24-day test.

The excretion of aldicarb in rats whose bile ducts had been cannulated was studied by Marshall and Dorough (1979). Two ARS-SD variety male rats were administered single oral 0.1 mg/kg bw doses of [^{14}C]thiomethyl-radiolabeled aldicarb in 0.2 mℓ vegetable oil by intubation. Urine, bile and feces were collected for 72 hours and analyzed for aldicarb and its metabolites. Within 48 hours of treatment, 92.6% of the radiolabel from the aldicarb dose had been recovered (Table III-11). Urine accounted for the largest portion (64%) of recovered ^{14}C-label, while fecal elimination accounted for <1%. No recovery values were given for the 72-hour post-treatment samples. Biliary excretion of the radiolabel accounted for 2.6, 9.5, 22.9, 28.1 and 28.6% of the dose at 3, 6, 12, 24 and 48 hours post-

TABLE III-9

Excretion of Radioactivity from Rats Treated with Carbonyl-C^{14} and Sulfur-35 Temik Sulfoxide[a,b]

	Cumulative % of Dose After Treatment with:				
	Carbonyl-C-14 Temik Sulfoxide			Sulfur-35 Temik Sulfoxide	
Time After Treatment	CO_2	Urine	Feces	Urine	Feces
2 hours	4.40	6.60	--	3.57	--
4 hours	8.10	12.80	--	15.38	--
8 hours	23.10	31.60	0.65	44.55	0.01
12 hours	27.75	39.10	1.46	54.10	0.33
24 hours	36.05	47.10	1.46	74.98	1.31
2 days	46.95	48.50	1.46	92.95	1.31
3 days	47.41	49.16	1.46	94.22	1.31
4 days	47.74	49.46	1.46	94.75	1.31
5-11 days	47.75	49.98	1.46	95.90	1.31

[a] Source: Andrawes et al., 1967

[b] Temik sulfoxide administered orally at 0.1 mg/kg

TABLE III-10

Excretion of Radioactivity over a 24-day Period from Rats Treated Orally with Sulfur-35 Temik at 0.4 mg/kg*

Days After Treatment	Cumulative % of Dose	
	Urine	Feces
1	68.14	3.35
2	81.57	5.14
3	84.73	5.97
4	86.19	6.64
5	87.51	6.64
6-24	91.61	6.64

*Source: Andrawes et al., 1967

TABLE III-11

Excretion of Radiocarbon from Bile-Duct-Cannulated Rats Treated Orally with a ^{14}C-Labeled Preparation of Aldicarb[a]

Hours After Treatment	Cumulative Percentage of Dose[b]			
	Bile	Urine	Feces	Total
3	2.8	--	--	2.8
6	5.9	--	--	5.9
12	11.9	35.6	0.0	47.5
24	25.7	54.3	0.0	80.0
48	28.6	64.0	0.0	92.6

[a] Modified from Marshall and Dorough, 1979

[b] Values are the mean of results from two rats

sample daily for a period of 9 days. The milk, which contained 62 ppb Temik equivalents, was administered by stomach tube in 3.5 mℓ doses (equivalent to 1 μg of Temik) daily. Urine samples were collected and combined 24 hours following each treatment and at 24-hour intervals for 5 days after the last treatment. The daily excretion of the radiolabel in urine was reported to be ~90% of the administered dose. Upon cessation of treatment, small quantities of radiolabel continued to be excreted in the urine for 5 days, by which time 96% of the total administered S-35 label from the milk had been excreted. This percentage may have been greater in actuality, since fecal samples were not collected and analyzed for radioactive residues.

Dorough et al. (1970) found that increasing the number of days that cows were exposed to aldicarb did not affect the nature or magnitude of residues eliminated in the milk, urine or feces on a daily basis. Three Holstein cows, each of which had calved 6-8 weeks previously and were in peak milk production, were administered equal molar quantities of Temik and Temik sulfone in acetone solution in a gelatin capsule containing crushed grain. Treatment was administered with a balling gun at 12-hour intervals (morning and evening milkings). Each cow received a separate dosage (0.12, 0.6 or 1.2 ppm in the diet). Nonradiolabeled insecticide was administered for the first 10 days of the experiment, followed by Temik-S-methyl-C^{14} and Temik sulfone-S-methyl-C^{14} for the following 14 days. Milk, urine and fecal samples were collected at 12-hour intervals (milking was conducted immediately following administration of the capsule). Most of the radiolabel was excreted in the urine, regardless of the dosage. In all three cows, 90% of the administered daily treatment was accounted for in the urine sample collected the following day. The authors noted that after 3 days post-treatment, respectively. The authors stated that the data from this experiment were indicative of enterohepatic recycling of aldicarb and/or its metabolites. It was pointed out that Andrawes et al. (1967) had recovered 5.1% of the administered dose in the feces of intact rats 48 hours after treatment. When compared with the 28.6% recovered in the same time span in this study, the data suggest that in intact rats the majority of the biliary metabolites are reabsorbed from the intestine and ultimately excreted in the urine.

Dorough and Ivie (1968) reported a study in which the excretion of aldicarb was monitored in both a cow and in rats. In the initial portion of the study, a lactating Jersey cow was administered a single oral dose of sulfur-35 radiolabeled Temik equivalent to 0.1 mg/kg bw (40 mg total dosage). Milk, urine and feces were then collected 3, 6 and 12 hours post-treatment, and at 12-hour intervals thereafter until no radiolabel could be detected in the eliminated product. The major route of excretion of the labeled Temik was found to be the urine. Within just 24 hours following treatment, ~83% of the administered radiolabel had been recovered in the urine. This amount had increased to 90% by 540 hours. By contrast, only 2.85% of the radiolabel was eliminated in the feces, all within 192 hours of treatment. Radioactive residues were present in a milk sample taken 3 hours post-treatment and were detected in all samples collected for a 540-hour period. Milk accounted for 3.02% of the total radiolabel (96.06%) recovered in 540 hours.

In the second part of the Dorough and Ivie (1968) study, two rats (sex and strain not specified) were administered a portion of the 3-hour cow milk treatment, the concentration of Temik-C^{14} equivalents in the milk, urine and feces was very close to the maximum detected at any time following administration, indicating a rapid stabilization of elimination by all three routes (Table III-12). An observed slight, but continuous, increase in the percentage of radiolabeled dose excreted in the urine was suspected to have been the result either of an increase in efficiency of excretion of daily doses by the cows or the release of radiolabeled products stored from the earlier feedings. A similar increase (from 1-2% of administered radiolabel the first day to 3-3.5% of the cumulative C^{14} treatments by day 14) was noted in the feces. When the approximate 1% radiolabel eliminated in the milk was combined with the urinary and fecal elimination percentages, the authors were led to conclude that dairy animals maintained on a continuous diet containing Temik would consistently eliminate 90% or more of the insecticide consumed daily.

Hicks et al. (1972) conducted a series of three experiments in which White Leghorn laying hens were administered oral doses of aldicarb-S^{35} or a 1:1 molar ratio of aldicarb-C^{14} and aldicarb sulfone-C^{14}. In the first experiment, 10 hens were given single 0.7 mg/kg bw oral doses of aldicarb-S^{35}. The dosages were administered in a gelatin capsule containing a small amount of laying mash. Feces were collected at 6-hour intervals for the first 12 hours post-treatment, and at subsequent 24-hour intervals. In a second test, six laying hens were fed single oral doses (0.7 mg aldicarb equivalents/kg bw) of a 1:1 molar ratio of aldicarb-C^{14} and aldicarb sulfone-C^{14} in gelatin capsules. Fecal samples were collected as in the first experiment. In both of these tests, the single 0.7 mg/kg oral doses were excreted rather rapidly, with 75% of the radiolabel being recovered

TABLE III-12

Excretion of Radioactivity by Cows Fed Temik-C^{14} Daily for 14 Days at Rates of 0.12, 0.6 and 1.2 ppm in the Diet[a]

	Percent of Total Dose for Each Treatment Level[b]								
	Milk, ppm			Urine, ppm			Feces, ppm		
Days Fed Insecticide	0.12	0.6	1.2	0.12	0.6	1.2	0.12	0.6	1.2
0.5	0.9	0.5	0.7	68.7	75.6	74.4	1.3	0.5	0.8
1	0.8	0.7	1.1	82.0	81.9	83.6	2.0	1.1	1.6
2	0.7	0.8	1.2	86.0	85.1	85.8	3.1	2.0	1.9
3	0.7	0.8	1.2	90.1	89.7	89.7	3.3	2.4	2.3
7	0.8	0.9	1.3	90.7	88.5	90.8	3.4	2.5	2.6
10	0.8	0.9	1.3	90.9	90.5	90.4	3.5	2.8	2.8
12	0.9	0.9	1.3	93.1	91.2	91.0	3.5	2.9	2.8
14	0.9	0.9	1.3	93.8	91.6	92.1	3.5	3.0	2.9

[a] Source: Dorough et al., 1970

[b] Calculations based on total dose consumed and total radioactivity eliminated by each indicated time.

within 24 hours of treatment and ~80% in 2 days. By the end of the tenth day post-treatment, 90% of the single oral dose of aldicarb-S^{35} had been eliminated from the body. No 10-day measurement was reported for the aldicarb-aldicarb sulfone mixture.

In a third experiment, Hicks et al. (1972) administered 1:1 molar ratio doses of aldicarb-C^{14} and aldicarb sulfone-C^{14} to hens every 12 hours for a period of 21 days. Groups of six birds each were given 0, 0.1, 1.0 or 20.0 ppm aldicarb in the diet (levels based upon an average daily feed consumption rate of 80 g/hen). The animals were fed a non-radioactive aldicarb-aldicarb sulfone mixture for 7 days prior to administering the radiolabeled mixture. The twice-daily dosages were administered in capsules containing one-half the total aldicarb equivalents required daily for the respective ppm dietary level. Fecal samples were collected just prior to each treatment. In this study, the pattern of elimination was found to be similar to that observed in the single dose experiments (Table III-13). After 8-10 days of treatment, an equilibrium was noted between the radiolabel ingested and excreted, with 80-85% of each daily dose being eliminated in the feces within the ensuing 24 hours. An exception was observed at the 20 ppm treatment level, however, at which only 60-65% was excreted on a daily basis. The authors could find no apparent reason for this difference although tissue accumulation was not disproven. When the treatment was discontinued, 90% of the total doses consumed were excreted within 1 week. The authors concluded from these studies that the rapid and thorough elimination of aldicarb would likely prevent the accumulation of large quantities of residues in the tissues.

TABLE III-13

Excretion of Radioactivity in the Feces of Hens Fed Equimolar Doses of Aldicarb-^{14}C and Aldicarb Sulfone-^{14}C in the Diet for 21 Days[a]

Days Fed Insecticides	Percent of Consumed Doses Excreted in the Feces[b] 0.1 ppm	1.0 ppm	20.0 ppm
0.5	76.0	76.2	64.7
1	75.3	69.8	62.7
3	77.5	71.9	64.9
11	87.9	88.6	69.8
19	83.3	82.7	70.1
21	84.9	82.6	71.0
21-day average[c]	82.2	80.3	67.5
Days After Last Treatment			
1	85.3	86.1	72.4
2	85.9	86.4	72.6
4	86.2	86.8	72.8
7	86.2	87.3	73.3

[a] Source: Hicks et al., 1972

[b] Based on total dose consumed and total radioactivity eliminated by indicated time after first treatment.

[c] Average of all daily values over the 21-day feeding period.

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as aldicarb from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to aldicarb is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels; what one eats; and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake.

Detailed information concerning the occurrence of, and exposure to, aldicarb in the environment is presented in another document entitled "Occurrence of Pesticides in Drinking Water, Food and Air" (Johnston et al., 1984). This chapter summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

In the Exposure Estimation section of this chapter, available information is presented on the range of human exposure and intake for aldicarb from drinking water, food and ambient air for the 70 kg adult human. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources.

Exposure Estimation

Drinking Water. The data obtained on levels of aldicarb in drinking water were not sufficient for use in determining the typical intake from this source.

Diet. The data obtained on levels of aldicarb in food were insufficient for use in estimating the typical dietary intake of aldicarb. However, a worst-case estimate of dietary intake [Theoretical Maximum Residue Contribution (TMRC)] was calculated based on tolerances set by EPA for aldicarb in and on raw agricultural commodities (Table IV-1) (FDA, 1981). The TMRC was derived by multiplying the tolerance level for each specific commodity by an EPA food factor (based on the percent of the diet each food represents) and by a factor of 1.5 kg for daily intake, and then summing across commodities. Using all commodities for which tolerances have been established (54% of the diet), the estimated TMRC was 106 μg/day (or 1.5 μg/kg/day for a 70 kg adult male). Using the tolerance level for potatoes only (potentially the major contributor to dietary exposure, and 5.43% of the diet), the estimated intake was 81.5 μg/day (or 1.2 μg/kg/day for a 70 kg male). Although the TMRC approaches this value, it would not be expected that an individual would be exposed to all of the foods listed in Table IV-1 at their tolerance levels.

Air. No data were obtained on levels of aldicarb in ambient air. Therefore, the intake of aldicarb from ambient air could not be estimated.

TABLE IV-1

Tolerances for Aldicarb In and On Raw Agricultural Products[a,b]

Commodity	Tolerance (µg/kg)
Bananas	300
Beans, dry	100
Beets	
sugar	50
sugar, tops	1,000
Cattle	
fat	10
meat by-products	10
meat	10
Coffeebeans	100
Cottoneed	100
Goats	
fat	10
meat by-products	10
meat	10
Hogs	
fat	10
meat by-products	10
meat	10
Horses	
fat	10
meat by-products	10
meat	10
Milk	2
Oranges	300
Peanuts	50
hulls	500
Pecans	500
Potatoes	1,000

TABLE IV-1 (cont.)

Commodity	Tolerance (μg/kg)
Sheep	
fat	10
meat by-products	10
meat	10
Soybeans	20
Sugarcane	20
fodder	100
forage	100
Sweet potatoes	100

[a] Source: 40 CFR 180.269, July 1, 1981

[b] For combined residues of aldicarb and its cholinesterase-inhibiting metabolites

Summary

Data on the intake of aldicarb from drinking water, food and ambient air are insufficient for use in determining which of the three sources is the major contributor to total intake.

References

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Johnston, P., F. Letkiewicz, D. Borum, et al. 1984. Occurrence of pesticides in drinking water, food and air. Interim draft report. Prepared by JRB Associates, McLean, VA, for Office of Drinking Water, U.S. EPA, Washington, DC.

V. HEALTH EFFECTS IN ANIMALS

General Toxicity

Acute Effects. NAS (1977) reports that the acute toxicity of aldicarb is probably the highest of any widely used insecticide. (Table V-1 provides LD_{50} values for a variety of species.)

The acute toxicity of aldicarb has been studied in a variety of laboratory animals, including rats (Striegel and Carpenter, 1962; Carpenter and Smyth, 1965; Weiden et al., 1965; Weil, 1968, 1973; Gaines, 1969; Weil and Carpenter, 1970), mice (Black et al., 1973), rabbits (Weiden et al., 1965) and chickens (West and Carpenter, 1965; Martin et al., 1981). Gaines (1969) determined LD_{50} values for 100 pesticidal compounds or their metabolites by administering single oral or dermal doses to adult Sherman rats of both sexes. In this study, technical grade Temik was administered in peanut oil via stomach tube or dermally as a solution in xylene. The female rats were found to be slightly more sensitive to Temik than were the males. Oral LD_{50} values were determined to be 0.8 and 0.6 mg/kg bw for males and females, respectively, while reported dermal LD_{50}s were 3.0 mg/kg bw for males and 2.5 mg/kg for females. The lowest doses reported to have killed rats were 0.5 mg/kg bw for oral administration and 2.0 mg/kg bw for the dermal route for animals of both sexes.

Other oral LD_{50} studies in rats produced similar but slightly higher values. When administered in a corn oil vehicle, LD_{50}s of 0.9 mg/kg bw for males and 1.0 mg/kg bw for females were derived (Carpenter and Smyth, 1965; Weiden et al., 1965). Range finding tests conducted by Striegel and Carpenter (1962) resulted in computation of an 0.93 mg/kg bw LD_{50} for the

TABLE V-1

Acute Toxicity of Aldicarb

LD_{50}	Route of Administration	Organism/Strain	Length of Exposure	Reference
0.93 mg/kg	oral	rats		Martin and Worthing, 1977
0.8 mg/kg (males)	oral	Sherman rats		Gaines, 1969*
0.65 mg/kg (females)	oral	Sherman rats		Gaines, 1969
0.9 mg/kg (males)	oral	rats (unspecified type)		Carpenter and Smyth, 1965
1 mg/kg (females)	oral	rats (unspecified type)		Weiden et al., 1965
3 mg/kg (males)	dermal	Sherman rats		Gaines, 1969
2.5 mg/kg (females)	dermal	Sherman rats		Gaines, 1969
0.3-0.5 mg/kg	oral	Swiss white mice		Black et al., 1973
2400 ppm diet	oral	Bobwhite quail (8 weeks old)	7 days	Martin and Worthing, 1977
9 mg/kg	oral	White Leghorn cockerel chickens		West and Carpenter, 1965

TABLE V-1 (cont.)

LD_{50}	Route of Administration	Organism/Strain	Length of Exposure	Reference
5.0 mg/kg	dermal	rabbits		Weiden et al., 1965
0.44 mg/kg	i.p.	rats (unspecified type)		Weil and Carpenter, 1970
8.3 ppm (LC_{50})	in water	rainbow trout		Martin and Worthing, 1977

*In the Gaines (1969) study, the lowest doses to kill rats were: oral, 0.5 mg/kg; dermal, 2.0 mg/kg.

male rat. LD_{50} values for aldicarb sulfoxide and aldicarb sulfone were determined to be 0.88 mg/kg bw and 25.0 mg/kg, respectively, in another study with rats (Weil, 1968).

When aldicarb was administered orally using other than a peanut or corn oil vehicle, the LD_{50} values were somewhat higher. Weil (1973) found the acute oral LD_{50} for Temik 10G to be 7.07 mg/kg bw in rats when administered as dry granules. Carpenter and Smyth (1965) placed 1 g of Temik 10G in 200 mℓ of water for 8 hours and then administered the formulation to rats. The resulting LD_{50} was determined to be 6.2 mg/kg bw.

In addition to the dermal study by Gaines (1969) mentioned above, the dermal toxicity to rats has been investigated in at least two other studies. Carpenter and Smyth (1965) conducted 4-hour skin penetration tests with rats utilizing Temik 10G applied as both dry formulation and with saline added. Following the 4-hour exposure period in which the test materials were taped to the skin, the dry formulation was found not to be as toxic as was the same mixture when wetted with saline. The respective LD_{50}s were 400 mg/kg bw for the wetted mixture and 3200 mg/kg for the dry application. Weil (1973), in a similar experiment, applied dry granules of Temik 10G or Temik 15G to the bellies of rats for 4 hours and found the LD_{50}s to be 4.58 and 6.32 g/kg bw for the 10% (10G) and 15% (15G) formulations, respectively.

The importance of the specific mode of dermal application has been further elucidated in a number of experiments on rabbits. The LD_{50} (24-hour) for a single application of a 50% solution of aldicarb in water to the skin of male rabbits was found to be 32 mg/kg bw (West and Carpenter, 1966a).

When the pesticide was applied as a 5% solution in propylene glycol, however, the LD_{50} was reduced to 5 mg/kg bw (Striegel and Carpenter, 1962). It was further demonstrated that a change in vehicle/carrier to dimethyl phthalate or a 5% toluene solution (4-hour exposure) resulted in LD_{50} values of 12.5 mg/kg bw and 3.5 mg/kg bw, respectively (Weiden et al., 1965; West and Carpenter, 1966a). By contrast, Carpenter and Smyth (1965) and Weil and Carpenter (1968c) reported an LD_{50} of 141 mg active aldicarb/kg bw in a 24-hour test in which dry Temik 10G was applied to the skin under adhesive tape.

The oral toxicity of aldicarb for other species of laboratory animals has also been reported. Black et al. (1973) found the acute oral toxic dose of technical grade aldicarb to be 0.3-0.5 mg/kg bw in Swiss white mice. Carpenter and Smyth (1965) noted that the LD_{50} for guinea pigs and rabbits fell in the same range as that for rats. West and Carpenter (1966a) reported the LD_{50} for white Leghorn cockerels to be 9 mg/kg bw (~10 times that observed in rats). The symptoms of aldicarb poisoning in chickens have been reported by Schlinke (1970) to be excessive salivation, dyspnea, stiffness and twitching of leg, wing and pectoral muscles. When 28-day-old Japanese quail (Coturnix coturnix japonica) were administered analytical grade aldicarb in corn oil solution by gelatin capsule at a dosage of 30 mg/kg bw (~3 times the LD_{50}), all birds died within 3 hours of treatment (Martin et al., 1981).

Acute toxicity resulting from exposure to aldicarb by other than oral or dermal routes has been reported. Weil and Carpenter (1970) determined LD_{50} values for rats intraperitoneally injected with aldicarb in corn oil or propylene glycol to be 0.44 mg/kg bw for both males and females. In inhalation studies with rats, mice and guinea pigs, Carpenter and Smyth (1965) found a concentration of 200 mg aldicarb dust/m³ to be highly toxic to all three species in a 5-minute exposure. At that level, rats and mice were observed to be more susceptible to the dust than were guinea pigs. The survival at a given concentration was found to vary with time. While rats appeared to be capable of surviving an aldicarb dust concentration of 6.7 mg/m³ for 15 minutes, 5 of 6 were killed by the same concentration in 30 minutes. By contrast, rats were able to survive 8 hours in atmospheres of saturated aldicarb vapors. It appears that aldicarb is somewhat less toxic as an aerosol than a dust, as attested by the observation that 2 of 6 rats were able to survive an 8-hour exposure to a 7.6 mg aldicarb/m³ aerosol. When the concentration of the aerosol was raised to 15 mg/m³, 5 of 6 animals exposed died within 4 hours.

Chronic and Subchronic Effects. Although a number of feeding studies of 3 months or less duration have been conducted (Weil and Carpenter, 1963; Carpenter and Smyth, 1965; Dorough et al., 1970; Nycum and Carpenter, 1970; Schlinke, 1970), only four long-term (chronic) studies could be located in the available literature (Weil and Carpenter, 1965, 1966, 1968c,d; Weil, 1975). Observed toxicity following dermal exposure also has been reported (Carpenter and Smyth, 1966; Pozzani and Carpenter, 1966). Table V-2 summarizes the data from available long-term and significant short-term studies.

Weil and Carpenter (1965) studied the effects of aldicarb administered in the diet of rats of an unspecified variety over a 2-year period. Four groups of rats, each group consisting of 20 males and 20 females, were maintained on diets containing aldicarb at levels of 0.005, 0.025, 0.05 or 0.1 mg/kg for 2 years. A control group of the same size was fed a similar

TABLE V-2

Chronic Toxicity of Aldicarb

Dose (mg/kg/day)	Duration	Route of Administration	Organism/Strain	Effects	Reference
0.1*	2 years	oral	rats (unspecified strain)	None	Weil and Carpenter, 1965
0.1	13 weeks	oral	CFE rats	No adverse effects	Weil and Carpenter, 1963
0.5	13 weeks	oral	CFE rats	Significant increase in mortality	Weil and Carpenter, 1963
0.3*	2 years	oral	Green Acres laboratory controlled rats	No adverse effects	Weil, 1975
0.3	2 years	oral (aldicarb sulfoxide)	Green Acres laboratory controlled rats	No adverse effects (some deaths in females at 0.6 mg/kg/day dosage)	Weil, 1975
2.4*	2 years	oral (aldicarb sulfone)	Green Acres laboratory controlled rats	No adverse effects	Weil, 1975
0.6	2 years	oral (1:1 aldicarb sulfoxide: sulfone mixture)	Green Acres laboratory controlled rats	No adverse effects (increased mortality within 30 days at 1.2 mg/kg/day)	Weil, 1975
0.1*	2 years	oral	beagle dogs	None	Weil and Carpenter, 1966
0.125	6 months	oral (aldicarb sulfoxide)	rats (unspecified strain)	None	Weil and Carpenter, 1968b
0.12	29 days	oral (drinking water -- 1:1 sulfoxide/ sulfone ratio)	Wistar rats	None	Mirro et al., 1982

*Highest dose administered

diet without the aldicarb. Concurrently, 32 rats per group (16 of each sex) were fed each diet for observation of shorter term effects. In this concurrent experiment, four animals of each sex were sacrificed following the sixth month of the experiment, and the remaining 12 rats of each sex were killed at the end of 1 year. Based upon measurements of food consumption, mortality and lifespan, incidence of infection, liver and kidney weights as percentage of body weight, body weight gain, maximum body weight, hematocrit, incidence of neoplasms, incidence of pathological lesions, and brain, plasma and erythrocyte cholinesterase levels, the aldicarb-treated animals were found not to differ significantly from controls for any of these parameters. The results of the 2-year feeding portion of this study are reported in the General Toxicity section of this chapter.

Another long-term feeding study using rats has been reported by Weil (1975). In this experiment, groups of 20 Greenacres Laboratory Controlled Flora rats of each sex were fed levels of 0.3 mg aldicarb/kg/day, 0.3 or 0.6 aldicarb sulfoxide/kg/day, 0.6 or 2.4 mg aldicarb sulfone/kg/day, or 0.6 or 1.2 mg of a 1:1 mixture of aldicarb sulfoxide and aldicarb sulfone/kg/day for up to 2 years. No adverse effects were observed at the 0.3 mg aldicarb/kg/day treatment level. However, the high dose of the aldicarb sulfoxide, aldicarb sulfone mixture resulted in increased mortality within the first 30 days, as well as a decrease in plasma cholinesterase activity and decreased weight gain in males. Some increase in mortality was also reported for females receiving the 0.6 mg/kg/day aldicarb sulfoxide treatment. No-observed-adverse-effect levels determined in this study were 0.3 mg/kg/day for aldicarb, 0.3 mg/kg/day for aldicarb sulfoxide, 2.4 mg/kg/day for aldicarb sulfone, and 0.6 mg/kg/day for the 1:1 mixture of aldicarb sulfoxide and aldicarb sulfone.

Weil and Carpenter (1966) reported a 2-year study in which beagle dogs were administered aldicarb (99.9% pure) in the diet. Four groups of dogs, three males and three females each, were fed dosages of aldicarb equivalent to 0, 0.1, 0.05 or 0.025 mg/kg/day. Based upon observations of body weight changes, appetite, mortality, histopathology, hematology, biochemistry, and terminal liver and kidney weights, there were no statistically significant deleterious effects found at any of the administered dosages. The no-effect level of 0.1 mg/kg/day for dogs is identical to the 0.1 mg/kg/day level determined for rats in the Weil and Carpenter (1965) experiment described previously, as well as in 90-day dog studies (Smyth, n.d.). It should be borne in mind, however, that neither of these Weil and Carpenter studies tested dosages above the 0.1 mg/kg/day level.

In studies using dosages more suitable for the analysis of cholinesterase inhibition, Weil and Carpenter (1968b,c) administered aldicarb sulfoxide or aldicarb sulfone in the diet to rats at dosage levels of 0, 0.125, 0.25, 0.5 or 1.0 mg sulfoxide/kg bw or 0, 0.2, 0.6, 1.8, 5.4 or 16.2 mg sulfone/kg bw. Groups of 15 animals of each sex were fed these aldicarb metabolites for a period of 6 months. Animals were sacrificed following 3- or 6-months of treatment for tissue examination and measurement of brain, plasma and RBC cholinesterase activity. The results of both the 3- and 6-month studies clearly indicated a substantial reduction (relative to controls) of cholinesterase levels at the three highest dosage levels for each compound when measured immediately upon cessation of feeding (Tables V-3 and V-4). The relative order of cholinesterase decrease was plasma > RBC > brain. No mortality or gross or microscopic tissue effects were noted, despite the reported substantial decrease in cholinesterase levels; however, some growth retardation was reported at the highest treatment dosages.

TABLE V-3

Inhibition of Cholinesterase in Rats (Male and Female) Fed Aldicarb Sulfoxide in the Diet for Three or Six Months[a]

Duration	Daily Dose in Diet (mg/kg)	Nature of Controls[b,c]	Percent Inhibition of Cholinesterases		
			Plasma (M, F)	Erythrocytes (M, F)	Brain (M, F)
		Study No. 1			
3 months	1.0	b	100,64	53,47	21,19
	0.5	b	52,54	20,30	0,5
	0.25	b	38,0	38,25	8,13
	0.125	b	45,15	2,19	7,6
6 months	1.0	b	73,66	75,68	16,20
	0.5	b	68,43	62,51	9,16
	0.25	b	39,9	44,20	3,5
	0.125	b	5,21	12,22	2,14
		Study No. 2			
3 months	1.0	b	76,61	58,62	0,22
		c	0,4	0,0	0,0
	0.5	b	44,39	28,46	-,3
		c	0,0	0,0	-,3
	0.25	b	42,-	44,18	-,-
		c	0,-	0,0	-,-
	0.125	b	9,-	-,0	-,-
		c	0,-	-,0	-,-
	0.0625	b	27,-	-,2	-,-
		c	9,-	-,6	-,-

[a] Modified from Wilkinson et al., 1983

[b] Percent inhibition vs. untreated control animals.

[c] Percent inhibition vs. treated self-controls after 1 day of nonfeeding of test agent at end of test period.

TABLE V-4

Inhibition of Cholinesterase in Rats (Male and Female) Fed Aldicarb Sulfone in the Diet for Three or Six Months[a]

Duration	Daily Dose in Diet (mg/kg)	Nature of Controls[b,c]	Percent Inhibition of Cholinesterases		
			Plasma (M, F)	Erythrocytes (M, F)	Brain (M, F)
		Study No. 1			
3 months	16.2	b	95,77	50,69	37,39
	5.4	b	66,62	40,52	15,27
	1.8	b	36,3	31,18	10,3
	1.2	b	-,-	-,-	-,-
	0.6	b	9,0	0,0	0,0
	0.2	b	5,0	2,13	2,6
6 months	16.2	b	82,85	76,84	46,50
	5.4	b	67,59	65,65	26,37
	1.8	b	14,24	28,26	15,16
	1.2	b	-,-	-,-	-,-
	0.6	b	0,6	8,9	2,9
	0.2	b	14,7	12,9	3,16
		Study No.2			
3 months	16.2	b	80,82	67,72	31,43
		c	0,0	0,0	0,0
	5.4	b	60,50	31,56	0,20
		c	16,0	0,0	0,6
	1.8	b	27,17	11,0	-,17
		c	2,0	6,0	-,0
	1.2	b	0,0	0,0	-,2
		c	0,0	0,0	-,0
	0.6	b	-,-	0,0	-,2
		c	-,-	-,-	-,0
	0.2	b	-,-	-,-	-,0
		c	-,-	-,-	-,3

[a] Modified from Wilkinson et al., 1983

[b] Percent inhibition vs. untreated control animals.

[c] Percent inhibition vs. treated self-controls after 1 day of nonfeeding of test agent at end of test period.

Using similar dosing regimens of aldicarb sulfoxide and sulfone for a 3-month treatment period, Weil and Carpenter (1968b,c) investigated cholinesterase activity depression in animals either sacrificed immediately upon cessation of feeding or placed on a control diet during a 1-day recovery period. The results of this study indicated a rapid recovery from the cholinesterase inhibition for all but the highest dosage levels for both test compounds. The Weil and Carpenter (1968b,c) studies have been utilized by the World Health Organization Committee on Pesticide Residues (FAO/WHO, 1980) to arrive at a 0.125 mg/kg bw NOEL for aldicarb sulfoxide in the rat.

A much larger number of short-term studies have been conducted using higher doses and a broader variety of test species. Weil and Carpenter (1963) reported a 93-day study in which aldicarb was administered in the diet of CFE male and female rats at dosages of 0, 0.02, 0.1 and 0.5 mg/kg/day. A significant increase in mortality (cause not specified) was noted at the high dose; mortality was further reported to be numerically, but not significantly, increased at the 0.1 mg/kg/day level. Upon examination of pathology, organ weight or plasma, erythrocyte, or brain cholinesterase levels, survivors at all dosage levels were found not to differ from controls with respect to these parameters. When aldicarb was fed at a level of 3.2 mg/kg/day, body weights of males and females were found to be depressed, while liver and kidney weights were not. Plasma cholinesterase activity was depressed in both males and females, but a reduction in erythrocyte cholinesterase activity was observed only in males.

In a shorter duration study with rats (Nycum and Carpenter, 1970), the effects of aldicarb, aldicarb sulfoxide and aldicarb sulfone were examined on groups of 10 (5 males and 5 females each) rats. Commencing on day 45 of age, the groups were administered the respective test compound in the feed for 7 days at dosages including 0.4, 1.0, 2.5 or 5.0 mg/kg/day. Parameters investigated included effects on body weight, liver and kidney weights, and brain, plasma and erythrocyte cholinesterase activity. Rats were said to tolerate >0.4 mg aldicarb sulfoxide/kg/day without effects on body weight, liver and kidney weight, or depression of brain, plasma or erythrocyte cholinesterase. Aldicarb sulfone was found to depress brain, plasma and erythrocyte cholinesterase at 5.0 mg/kg bw. A statistically significant decrease in brain cholinesterase was observed in female rats administered the 2.5 and 1.0 mg/kg bw dosages. [Note: No further results were reported. However, the original paper was not available for this study and a secondary reference (U.S. EPA, 1975) was therefore relied upon for the limited information presented above.]

In a study utilizing a route of exposure particularly relevant to this assessment document, Mirro et al. (1982) administered a 1:1 ratio mixture of aldicarb sulfoxide and aldicarb sulfone in drinking water to young Wistar rats. Groups consisting of 10 animals of each sex were provided water containing concentrations of 19.2, 4.8, 1.2, 0.3, 0.075 or 0.0 ppm of the treatment mixture. Individual dosage levels based upon the nominal concentrations used and measured initial weights of the animals ranged from 0-1.67 mg/kg/day for males and 0-1.94 mg/kg/day for females. Blood samples were taken after 8, 15 and 29 days of treatment and analyzed for plasma and erythrocyte cholinesterase levels. Brain cholinesterase determinations were made at sacrifice (29 days after initiation of treatment). Plasma cholinesterase was reduced (64-77%) in all animals at the 19.2 ppm dosage. The 4.8 ppm treatment level of the sulfoxide:sulfone mixture was reported to cause a statistically significant (28% mean) reduction in plasma cholinesterase only in male rats and only following 8 days of treatment. RBC cholinesterase activity was likewise reduced at all sampling periods in all 19.2 ppm treated rats, with reported decreases ranging from 48-63%. A reduction of 24% erythrocyte cholinesterase was further observed in males at the 4.8 ppm dose level following 29 days of exposure. The only reported statistically significant reduction in brain cholinesterase was a 10% decrease in female rats following 29 days of treatment at the highest dosage level. No mention of symptoms associated with any of the observed cholinesterase inhibition was made. Body weight changes and water consumption were also reported to be reduced significantly in both sexes at 7, 14, 21 and 29 days into treatment, as was food consumption during the same time in males. Based upon a reduction in plasma and erythrocyte cholinesterase activity, a NOEL of 1.2 ppm (0.12 mg/kg bw) would be appropriate from the data presented. It should be noted that this NOEL is based upon a 1:1 mixture of aldicarb sulfoxide and aldicarb sulfone. Therefore, given the known higher toxicity of the sulfoxide moiety, a lower NOEL might be expected from similar administration of the sulfoxide alone.

Dorough et al. (1970) administered lactating Holstein cows Temik in their diet in a two-part experiment. In a pilot study to determine the effect of Temik on the general health of a cow, a single 645 kg cow was given Temik and Temik sulfone at a rate equivalent to 1.2 ppm Temik (0.042 mg/kg bw) in the diet for 10 days. Daily blood samples were withdrawn 6 hours after the morning milking and immediately assayed for RBC and plasma cholinesterase activity. The animal was milked at 12-hour intervals. The results of this pilot study indicated that feeding a dairy cow 1.2 ppm Temik equivalents would not cause any visible ill effects to the animal. Assays indicated that blood cholinesterase levels were not reduced by the treatment, and milk production (quantitative) remained constant during the treatment.

In the second part of the same study, Dorough and his co-workers fed three cows separate dosages of a Temik-Temik sulfone combination for a period of 14 days. The treatment dosages were administered twice daily with a balling gun at 12-hour intervals in the form of a gelatin capsule containing crushed grain. Individual doses of Temik equivalents were 0.12 ppm (0.006 mg/kg bw) for one cow, 0.6 ppm (0.027 mg/kg bw) for a second cow, and 1.2 ppm (0.052 mg/kg bw) for the third animal. As in the pilot study, blood was taken from each animal on a daily basis throughout the treatment period. The blood was withdrawn 6 hours after the morning milking and immediately assayed for plasma and RBC cholinesterase activity. All animals were milked regularly at 12-hour intervals. In this experiment, no apparent harmful effects on any of the test animals were noted. Regardless of the level of administered dose, blood cholinesterase levels were the same both before and during treatment. Milk production, feed consumption and quantity of excretory products were reported to have remained stable throughout the experiment. A conclusion reached by the authors was that, with only minor exception, it was apparent that the continuous exposure of dairy animals to Temik in the diet does not significantly alter its fate compared to single exposure.

The toxic effects of aldicarb in chickens was evaluated by Schlinke (1970). In this experiment, groups of five White Leghorn chickens, 6-7 weeks old, were treated with oral doses of 1.0, 2.5 or 5 mg aldicarb/kg/day. Individual dosages were administered in gelatin capsules or by oral drench for a period of 10 days. Animals were observed for body weight gain and mortality. No ill effects were reported among the chickens receiving the 1.0 mg/kg/day dosage. Percent body weight gain for these animals was 44%, compared to 49% in the control group. The 2.5 mg/kg/day dosage level proved fatal to two chickens, one after receiving the first dose and a second following the third dose. Body weight gain among survivors in this group was 30%, while weight gain among a corresponding control group was 40%. Of the birds receiving 5 mg aldicarb/kg/day, none survived past the third dosing. One died following administration of the first dose, one following the second dose, and the remaining three after administration of the third dose.

Johnson and Carpenter (1966) administered daily oral doses of 2.25 mg/kg or 4.5 mg/kg to groups of six adult chickens for 30 days and examined the animals for signs of neurotoxicity. Neither delayed ataxia nor apparent limb paralysis were evident either during the dosing period or within 30 days following the administration of the last dose at either level of aldicarb tested. When six chickens were administered 9.0 mg/kg [the LD_{50} for White Leghorn cockerels reported by West and Carpenter (1965)], four died within 2 weeks of initiation of treatment without displaying overt ataxia or limb paralysis.

Carpenter and Smyth (1965) reported the dosing of cats with 0.5, 1.0 or 1.5 mg aldicarb/kg/day for multiple doses, with a 7-8 day interval between doses. These authors reported no evidence of tolerance through continued exposure, as death following administration of the third dose was as prompt as the death observed after administration of the first dose.

The toxic effects of short-term dermal exposure to aldicarb have also been investigated (Carpenter and Smyth, 1966; Pozzani and Carpenter, 1966). The toxic effects of aldicarb administered dermally for a period of 15 days were investigated by Carpenter and Smyth (1966). In this study, Temik 10G (10.5% active granular formulation) was administered to male albino rabbits by application of wetted gauze to abraded skin areas for 6 hours/day through a consecutive 15-day period. Dosage levels of 0.05, 0.10 and 0.20 g/kg were tested. Criteria used to assess the toxicity of Temik were total weight gain, food consumption, liver and kidney weights, plasma and erythrocyte cholinesterase activity, and histopathological examination of liver, lung, kidney, heart, muscle, thyroid and skin tissue. A course of hematology was also run, as were kidney function (blood urea nitrogen) and liver function (serum glutamic oxalacetic and pyruvic transaminase) tests. The only parameter significantly affected was body weight gain, as depressed gains were observed in the groups administered 0.1 and 0.2 g Temik/kg. Plasma cholinesterase activity was also reported to be depressed at these treatment levels.

In a test to simulate more closely environmental exposure conditions, Pozzani and Carpenter (1966) dermally exposed groups of six female albino rats (with ventral surfaces shaved free of hair) to top soil treated with

Temik 10G for a period of 28 days. The Temik was incorporated into the soil to a depth of 6 cm at application rates of 100 and 500 lb/acre. The authors noted that all animals survived this experiment with no adverse effects; no gross lesions or adverse body weight changes were observed. It should be noted that the soil application rates used in this study represented rates 1 and 5 times the recommended usage.

Pozzani and Carpenter (1968) noted that aldicarb (0.7 mg/kg) in saline injected intradermally to male guinea pigs exhibited no sensitizing properties.

Target Organ Toxicity

As previously discussed, the primary mode of toxicologic action of aldicarb is via complexing with the enzyme responsible for the breakdown of the chemical neurotransmitter acetylcholine. There is no other evidence of direct toxic action on specific organ systems aside from the anticholinesterase activity of the compound or its metabolites.

Other Effects

Carcinogenicity. Aldicarb has been found to be noncarcinogenic to mice in a skin painting study (Weil and Carpenter, 1966) and to both mice and rats in feeding studies (Weil and Carpenter, 1965; NCI, 1979) at the doses, and under the conditions, tested.

Weil and Carpenter (1966) conducted a skin painting study using male C3H/H3J mice. Female mice were not employed for this test due to the incidence of spontaneous mammary tumors, particularly in breeding females. Mice were administered the aldicarb in the form of applications of a 0.125% concentration to hair-free skin on the backs of the animals twice per week for up to 28 months or until death. When compared with controls (positive control group painted with cholanthrene), aldicarb was determined to be noncarcinogenic under the conditions of the experiment.

In a 2-year feeding study, Weil and Carpenter (1965) administered equivalent doses of 0.005, 0.025, 0.05 or 0.1 mg aldicarb/kg/day in the diet to an unspecified strain of rats. The incidences of tumors were determined not to be significantly greater than those of control groups. Weil (1975) also reported no adverse effects in Greenacres Laboratory Controlled Flora rats fed 0.3 mg/kg/day for 2 years, although it is not clear whether this particular study was designed specifically as a cancer experiment.

NCI (1979) conducted a bioassay of aldicarb for possible carcinogenic effects in rats and mice. Test groups of 50 male and 50 female F344 rats and the same numbers of male and female B6C3F1 mice were administered doses of either 2 or 6 ppm in a diet containing 2% corn oil for 103 weeks. The animals were then observed for an additional 0-2 weeks and killed. Matched controls were comprised of 25 untreated rats and 25 untreated mice of each sex. No tumors occurred in either the rats or mice that could be clearly determined to be the result of the aldicarb administration.

In the NCI (1979) bioassay, dose related adenomas or carcinomas of the pituitary were observed in female rats ($p=0.048$); however, the incidences of these tumors were not significantly higher than those observed in the corresponding control group. Similarly, fibrosarcomas or sarcomas of subcutaneous tissue were observed to occur in male mice at incidences that appeared to be dose related (p=0.043), but these incidences were also found not to be significantly higher than in the corresponding control group. It should be noted that the incidence of pituitary tumors in historical-control female F344 rats at the laboratory conducting the bioassay was also reportedly high. Consequently, the occurrence of the pituitary tumors in female rats and subcutaneous tissue tumors of male mice could not be clearly related to the aldicarb administration. Since no tumors occurred at statistically significant levels in either the rats or mice tested, it was concluded that, under the conditions of that bioassay, technical-grade (99+%) aldicarb was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

Quarles et al. (1979) tested a number of pesticides, including aldicarb, and their N-nitroso derivatives for transforming and tumorigenic activity. The exact purity of aldicarb was not specified, although it was indicated to be >95%. In the host-mediated assay portion of this study, pregnant hamsters were given i.p. injections of 0.001 or 0.005 mg aldicarb/kg bw administered in a nontransforming solvent. Injections were given on day 10 of gestation, and fetal cell cultures prepared on day 13. In evaluation of this test, colonies were considered to have been transformed if the cells had clearly lost orientation and were criss-crossed or multilayered. At the same time cultures were plated for plating efficiency and determination of transformation, cells were also tested for growth in 0.3% agar. To test for tumorigenicity, approximately $1x10^6$ transformed or untransformed cells were injected s.c. into young adult nude (athymic) mice. These 4- to 6-week-old mice were then maintained in groups of 3-6/standard polycarbonate cage, and observed for 6-12 months for tumor formation. To test for spontaneous transformation, fetal cell cultures were handled at intervals throughout the study and examined according to standard test procedures. Of nearly 38,000 colonies examined, none revealed evidence of morphological transformants and no growth of cells in 0.3% agar was observed. Therefore, the spontaneous transformation rate was determined to be insignificant in this assay. Likewise, the solvents used in this experiment were similarly tested and, of approximately 22,000 colonies examined, no induction of morphological transformation or growth of cells suspended in 0.3% agar was observed following treatment of pregnant hamsters with the test solvents. For the transplacental host-mediated assay, dosages chosen for the various test compounds were the greatest nonlethal dose tested that did not exceed 0.3 mg/kg bw (0.001 and 0.005 mg/kg bw for aldicarb and 0.002 mg/kg for nitrosoaldicarb). While aldicarb showed no transforming activity at the dosages tested, nitrosoaldicarb was found to induce transformations at the rate of 0.5%, and the nitrosated compound was further found to induce cell growth in the 0.3% agar (aldicarb at 0.005% produced no growth and was not tested at 0.001 mg/kg). When clones isolated from subcultures 5-7 were tested for tumorigenicity in the nude mice, none of the four mice inoculated developed tumors; however, tumors were observed in 2 of 3 mice tested with nitrosoaldicarb. The study concluded that aldicarb was inactive and induced neither morphological transformants nor cells that grew in agar, while nitrosoaldicarb induced morphological transformants that grew in agar and were tumorigenic in nude mice. Although the doses were noted, the actual amount of chemical reaching each embryo was not determined.

The possibility that N-methylcarbamate insecticides might interact with nitrites in the environment or _in vivo_ to form N-nitroso compounds, and the known carcinogenicity of N-nitroso derivatives of carbaryl and benzthiazuron, prompted Lijinsky and Schmähl (1978) to investigate the carcinogenicity of the N-nitroso derivatives of aldicarb and a number of other carbamates. These researchers reported the administration of nitrosoaldicarb to two groups of 8- to 10-week-old female Sprague-Dawley rats at dosage levels of 10 or 20 mg/kg bw. The treatment was administered weekly by stomach intubation using olive oil as a vehicle. The 20 mg/kg dose applications were originally scheduled to last 10 weeks, but this level proved lethal to 10 of the rats and was reduced by half after just 2 weeks. The two animals surviving the two 20 mg/kg doses of nitrosoaldicarb received no further treatments. The 10 mg/kg dose level was administered to 12 other female rats for 9 weeks, but treatment was similarly discontinued after just 9 (of the scheduled 20) weeks, due to the deaths of 9 of the test rats, presumably as a result of high parent compound toxicity. All five surviving animals from the two groups were allowed to remain alive until spontaneous death or until moribund. Each animal was then subjected to complete histological examination and all tumors were fixed. All five animals developed tumors of the forestomach (Table V-5). Although low survival of the test rats precluded a full assessment of the carcinogenicity of nitrosoaldicarb, the authors stated that this derivative is a potent carcinogen based upon the observation that two treatments (9.6 mg total) were sufficient to induce stomach tumors in both animals that survived the 20 mg/kg bw doses. No tumors of the non-glandular stomach were found in any of the 40 control rats (all males) treated with the vehicle, only.

TABLE V-5

Mortality and Tumor Incidence of Rats Treated with Nitrosated Aldicarb[a]

Compound	Weekly Dose (mg/kg)	Total Dose (mg/kg)	Survival of Rats at Week							No. of Rats with Stomach Tumors	
			0	20	40	60	80	100	120	Carcinomas	All Tumors
Nitrsoaldicarb[b]	20	40	12	2	2	2	2	0		2	2
	10	90	12	3	3	3	3	2	0	2	3
Corn oil control[c]			40	40	40	35	14	7	0	0	0

[a] Modified from Lijinsky and Schmähl, 1978

[b] All animals receiving the nitrosoaldicarb treatment were females.

[c] All animals receiving the corn oil control were males.

An interesting observation was made by Lijinsky and Schmähl (1978) that, at lower doses, the carcinogenic potency (based upon the total number of animals with tumors and the number of carcinomas induced) among the tested N-nitroso derivatives of N-methylcarbamate insecticides is in a direction opposite to that of their mutagenic potency in bacteria. These authors concluded that if nitrosomethylcarbamates are formed by the reaction of the parent insecticides with nitrite in either the environment or the human stomach, there could be some increase in the risk of cancer. The degree of risk, however, would be difficult to assess accurately, and cannot reliably be quantitatively based upon known mutagenic effectiveness in bacteria. (See the Target Organ Toxicity section of this chapter for additional information.)

The studies of nitrosoaldicarb are of significance, since under the temperature and pH conditions of the human stomach, and in the presence of nitrite, the N-nitroso derivatives of N-methyl carbamate insecticides, such as aldicarb, are readily formed (Elespuru and Lijinsky, 1973). Further, nitrite is a commonly used food additive, particularly in foods of animal origin, and may also become an inadvertent contaminant of food intended for human consumption (Kolari and Aunan, 1972; Phillips, 1971). Nitrite is also normally present in human saliva at concentrations of 1-10 ppm (Varady and Szanto, 1940; Eisenbrand et al., 1974). When residual levels of aldicarb or other N-methyl carbamates in plants or drinking water are consumed by humans, the formation of carcinogenic nitrosamines are a distinct possibility.

Mutagenicity. Conclusive evidence on the mutagenicity of aldicarb is not yet available. U.S. EPA (1975) cited an unpublished report by Weil and Carpenter (1974a) that 0.7 mg aldicarb/kg bw of rats caused no adverse effects in the dominant lethal mutagenicity test. Ercegovich and Rashid (1973) evaluated 70 pesticides and their related degradation products for mutagenic effects in five strains of *Salmonella typhimurium* employing the procedures of the Ames test, and found aldicarb to be weakly mutagenic only without activation by liver microsomal enzymes.

Blevins et al. (1977) treated normal human skin cells with six insecticide esters of N-methyl-carbamic acid (including aldicarb) or their N-nitroso derivatives. DNA from the cells was then sedimented in alkaline sucrose gradients at various times post-treatment. Weight-average molecular weight values obtained from velocity of sedimentation data indicated numerous single-strand breaks in the DNA of the aldicarb nitroso derivative-treated cells, but not in cells treated with the parent compound. The authors attributed the results to either direct induction of many single-strand breaks in the DNA or the formation of numerous alkali-sensitive bonds that resulted in breaks when the cells were lysed on top of the alkaline gradients. The mode of action of the DNA-damaging agents, including the aldicarb nitroso derivative, did not result in long or short repair, but rather the apparent formation of alkali-sensitive bonds [as is the case with nitrosocarbaryl, shown by Elespuru et al. (1974) to be a powerful mutagen], which evidently remain in the DNA for long times. The observations of Blevins and his co-workers suggest that human cellular DNA *in vivo* is altered irreversibly by nitrosated N-methyl carbamate insecticides. This is significant for reasons discussed in the General Toxicity section of this chapter.

In a related experiment, Seiler (1977) took 37 nitrogenous pesticides, including aldicarb, and nitrosated them with sodium nitrite *in vitro*. They then tested the nitrosated compounds for mutagenic activity in the bacterial spot test with *Salmonella typhimurium* his G46. Nitrosoaldicarb was determined to be active (although "not exceedingly") in the bacterial plate test. In this experiment, most of the compounds having a positive plate test were then tested *in vivo* using the micronucleus test; however, due to its high toxicity, aldicarb could not be administered and was therefore not tested *in vivo*.

Teratogenicity. Of the limited studies available on the subject, none indicated any teratogenic effects associated with exposure to aldicarb.

The potential of aldicarb as a teratogen was investigated in rats by Weil and Carpenter (1964). Pregnant rats were administered dosages of 0.0, 0.04, 0.20 and 1.0 mg aldicarb/kg bw in the diet. The rats were further divided into three groups: Group 1 rats were fed aldicarb in the diet throughout pregnancy or until the pups were weaned; Group 2 rats were administered aldicarb from the day the vaginal plug first appeared through the seventh day; and Group 3 received aldicarb from days 5 through 15 of gestation. No congenital malformations were reported for any of the treated groups, and body weights of both the mothers and pups were normal. Although the 1.0 mg/kg dose level was at or near the reported single dose LD_{50} value for rats (Striegel and Carpenter, 1962; Carpenter and Smyth, 1965; Weiden et al., 1965; Gaines, 1969), no significant effects were observed concerning fertility, gestation, viability of offspring or lactation.

In a study conducted by the International Research and Development Corporation (IRDC, 1983), groups of 16 pregnant Dutch Belted rabbits each were administered singly daily doses of aldicarb to determine the teratogenic potential of that insecticide. Treatment levels of 0, 0.1, 0.25 or 0.50 mg/kg/day were applied via gavage to the respective groups on days 7 through 27 of gestation. Fetuses were removed surgically by Cesarean section on day 28 of gestation and examined for teratologic effects.

One spontaneous abortion each was reported in the 0.25 and 0.5 mg/kg/day groups. Although viable fetuses and total implantation values were less for all treatment groups than for controls, the values fell within historical control ranges. No "meaningful" differences in fetal malformations or developmental variations between the control and treated groups were reported.

Weil and Carpenter (1964) conducted a 3-generation study of the effect(s) of aldicarb on reproductive performance in rats. The insecticide was incorporated into the diet of the parent generation animals at levels of 0.05 or 0.1 mg/kg/day for 84 days prior to mating. Similar dosages were fed to subsequent generations. Progeny (112 days old) were mated and their offspring used as parents for the F_3 generation pups. Comparison of indices for fertility, gestation, viability, lactation, mean weight of pups, micropathology of F_3 generation weanlings and 90-day-old F_3 adults revealed no statistically significant differences relative to controls, nor was food consumption affected by either dosage level.

Proctor et al. (1976) investigated the effects of a number of methyl carbamate and organophosphate insecticides on teratogenicity and embryo NAD levels. In this experiment, fertile white Leghorn eggs were injected with 1 mg of aldicarb in a 30 µℓ methoxytriglycol solution. The injection was made directly into the yolk following a 4-day incubation period at 37°C and 73% relative humidity, and the site of injection on the shell sealed with paraffin wax. On day 12 following injection, six embryos were removed and NAD levels examined. On day 19 after injection, the remaining embryos (at least 10) were examined for teratogenic signs. NAD levels were found to be 100% relative to controls, and although there were slight differences in body weight, body length and leg length from controls, no teratogenic effects (straight legs, abnormal feathers or wry neck) were observed in any of the embryos exposed to aldicarb.

Other Reproductive Effects. In a study designed to determine the metabolic fate of Temik in lactating cows, Dorough and Ivie (1968) administered a single dose of 0.1 mg radiolabeled aldicarb (Temik-S^{35})/kg bw in crushed grain to a lactating Jersey cow. The total amount of Temik consumed was 40 mg. Milk, urine and feces were then collected at 3, 6 and 12 hours post-treatment and at 12-hour intervals thereafter until no radiolabeled residues could be detected. A portion of the 3-hour milk sample, which contained 62 ppb Temik equivalents, was fed daily to two rats via stomach tube for 9 days. The doses received by each rat were equivalent to 1 µg Temik/day. Within the 540 hours of the experiment, 3.02% of the total 40 mg dose was eliminated in the milk. Although the milk contained 62 ppb Temik just 3 hours following treatment, the Temik equivalents had declined to 10, 1 and 0.1 ppb after 84, 276 and 540 hours postdosing, respectively.

The rats fed daily doses of the Temik-S^{35} metabolite-contaminated milk excreted ~90% of the dose received in the urine. By 5 days after cessation of the milk doses, 96% of the total Temik metabolites had been excreted. No adverse effects in either the lactating cow or the rats were mentioned, and the authors concluded that nothing in the experiment indicated existence of residual hazards. They stated further that if Temik and its metabolites were present in milk at very low levels, and if the milk was consumed by other animals, the residues would probably be excreted from the body rather rapidly.

In a follow-up study, Dorough et al. (1970) fed lactating Holstein cows 0.12, 0.6 or 1.2 ppm radiolabeled aldicarb (Temik-C^{14}) for 14 days. This dosage regimen had no apparent adverse effects on any of the cows. Blood cholinesterase levels remained the same as pre-treatment levels throughout the period of treatment. There were also no effects on milk production, feed consumption or quantity of excretory products throughout the experiment. The levels of radiolabeled residues in the milk are given in Table V-6. The relative concentrations of Temik metabolites remained reasonably constant throughout the 14-day feeding period, indicating that metabolism of aldicarb was not altered by increasing the concentration in feed from 0.12 to 1.2 ppm. Approximately 1% of the total dose was eliminated in the milk in this experiment.

There have been two recent studies (Cambon et al., 1979, 1980) in which fetal and maternal brain blood and liver AChE activity has been examined following administration of aldicarb. Cambon et al. (1979) administered

TABLE V-6

Aldicarb-C^{14} Equivalents in Holstein Cows Fed Radiolabeled Temik in the Diet*

Dosage Level (ppm)	Range of C^{14} Residues (ppb)	Average Residue Level (ppb)
0.12	0.9-1.9	1.4
0.6	5.0-6.5	5.7
1.2	12.1-15.3	13.3

*Adapted from Dorough et al., 1970

analytical grade (99%) aldicarb to nulliparous pregnant female Sprague-Dawley rats (3 groups of 8 each) at dosage levels of 0.001, 0.01 or 0.1 mg/kg bw on day 18 of gestation. Treatments consisted of single doses administered by gastric intubation, and the animals were killed by decapitation 1, 5 or 24 hours following treatment. Blood, brain and liver samples of both dams and fetuses were analyzed for AChE activity.

Table V-7 reflects the results of this study. Signs of poisoning were manifested within 5 minutes of the 0.1 mg/kg administration. At this dosage level, all of the tissue samples taken 1 and 5 hours following treatment displayed a significant decrease in AChE activity. A decrease in acetylcholinesterase activity was still evident in both maternal and fetal blood 24 hours after administration of the higher dosage levels. It should be noted, as the authors pointed out, that AChE activity was inhibited in the fetus just 1 hour following a dosage 1000 times lower than the LD_{50} for aldicarb in the adult. This decrease was noted in the blood, brain and liver of the fetus, although in adults only the liver manifested a decrease in AChE activity following administration of this 0.001 mg/kg dose. Acetylcholinesterase activity in the fetus was significantly lowered at all dosages of aldicarb. Further, in a number of instances the inhibition of AChE activity was greater in fetal than maternal tissue, leading the authors to suggest possible accumulation in fetal tissues.

In a subsequent study, Cambon et al. (1979) administered by gastric intubation a single dose of 0.1 mg aldicarb/kg bw to six nulliparous pregnant Sprague-Dawley rats on day 18 of gestation. The rats were killed by decapitation 1 hour after treatment. The acetylcholinesterase enzymes

TABLE V-7

Activity of Acetylcholinesterase in Maternal and Fetal Tissues from Rats Given Aldicarb by Gastric Intubation[a]

Dose (mg/kg)	Time (hours)	AChE units per gram of protein		AChE units per gram of organ			
		Maternal Blood	Fetal Blood	Maternal Brain	Maternal Liver	Fetal Brain	Fetal Liver
Control	18th day	22.9±1.47	24.0±2.42	9.41±1.45	5.89±0.86	1.45±0.06	1.75±0.07
	19th day	23.7±1.06	17.7±1.48	9.30±1.70	3.70±1.18	1.39±0.10	1.35±0.11
0.001	1	22.9±1.46	21.1±1.53[b]	8.93±2.64	4.88±0.82[b]	1.18±0.15[c]	1.47±0.12[c]
0.01	1	22.0±2.48	17.9±5.50[d]	8.02±2.00	4.22±0.49[c]	1.00±0.10[c]	1.33±0.31[c]
	5	18.7±2.40[d]	13.2±1.90[d]	9.50±1.30	4.20±0.80[d]	1.30±0.17[b]	1.50±0.10[c]
	24	20.4±3.68[b]	13.2±2.22[c]	8.16±2.13	3.13±0.72	1.19±0.24[b]	1.03±0.15[c]
0.10	1	16.0±3.73[c]	12.7±1.93[c]	6.99±1.84[b]	2.81±0.61[c]	0.83±0.09[c]	1.95±0.19[c]
	5	15.3±2.20[c]	14.5±2.08[c]	7.48±0.82[d]	3.55±0.77[c]	1.07±0.06[c]	1.55±0.20[b]
	24	22.0±1.80[b]	13.6±0.95[c]	8.30±1.80	3.19±1.25	1.25±0.18	1.08±0.07[c]

[a] Source: Cambon et al., 1979

[b] Significantly different than control value at $p<0.05$.

[c] Significantly different than control value at $p<0.001$.

[d] Significantly different than control value at $p<0.01$.

from the brains of mothers and fetuses were separated by electrophoresis on a polyacrylamide gel and stained. The stain intensity of the various electrophoretic fractions was then measured using a densitometer. A significant inhibition of both maternal and fetal cerebral AChE was observed, as was the case in their 1979 experiment. The existence of three distinct isoenzymes was noted. The aldicarb treatment resulted in a significant lowering in the dams of the least mobile of the three (isoenzyme 1). Both isoenzymes 1 and 2 underwent a decrease in the fetuses. The authors suggested that the greater inhibition of fetal (when compared with maternal) brain AChE activity in their 1979 experiment might be due to binding of the inhibitors in the fetus for two of the isoenzymes, while the same dose only decreases the first isoenzyme in the mother. The authors concluded that this study tended to support the hypothesis that the sensitivity difference observed in maternal and fetal AChE to insecticides is in the specific affinities of carbamate derivatives, such as aldicarb, for each fetal and maternal isoenzyme.

VI. HEALTH EFFECTS IN HUMANS

Clinical Case Studies and Accidental Poisonings

Lee and Ransdell (1984) reported the death of a California farmworker who had been working with aldicarb. A 20-year-old Mexican male, assigned to load granulated aldicarb (formulated as Temik 15G) into a hopper, was observed by an overseer to be lacking proper protective equipment, and was subsequently given an organic vapor respirator, goggles and paper coveralls. The worker then returned to what was believed to be his first assignment as a pesticide loader without any observable signs or symptoms of problems. In all, he was believed to have opened as many as 14 bags of Temik, the empty packaging from which was burned ~200 feet from the loading site.

Approximately 2 hours after the worker had begun to load the Temik, his body was discovered between a tractor and its trailing disc blades by the tractor driver, who had stopped along the border of a field adjacent to the loading site to avoid irrigation equipment. The victim was pronounced dead on arrival at a local hospital. Initial postmortem procedures were performed by the coroner, without the knowledge that the victim had been working with a pesticide. At autopsy, multiple trauma was present, and the immediate cause of death was determined to be massive crushing chest injuries. A single blood sample was preserved and subsequently examined for red cell cholinesterase activity, which was determined to be 0.37 delta pH units (normal range is 0.55-1.25 delta pH units). The reported inadvertant use of sodium fluoride, a known inhibitor of cholinesterase activity, as an anticoagulant and blood preservative makes this reported blood value invalid, however.

Upon belated arrival of information indicating possible pesticide exposure, liver, kidney and skin samples were taken for residue analysis. Residues of aldicarb, aldicarb sulfoxide and aldicarb sulfone were quantitated using high-performance liquid chromatography and an ultraviolet fluorescence technique. Detectable levels of total aldicarb derivatives (aldicarb, aldicarb sulfoxide and aldicarb sulfone) were found in all tissues analyzed (Table VI-1). The skin of the hand had the highest concentration of aldicarb (0.492 ppm), while the kidney had the greatest concentrations of the sulfoxide and sulfone, 0.261 and 0.422 ppm, respectively. Extremely little or none of the parent compound was found in the blood, liver or kidney. The high concentration of aldicarb sulfoxide and sulfone found in renal tissue was reported to be evidence that excretion was already occurring at the time of death.

Lee and Ransdell (1984) further estimated the body burden of aldicarb, based upon total body water distribution, to be 18.2 mg. This was divided by the weight of the victim (66.28 kg) to get a 0.275 mg/kg bw "dose". Since the tissue samples were refrigerated (but not frozen) for ~10 days, however, it was believed that some hydrolysis and enzymatic loss probably occurred, thus suggesting that the measured residue levels might have been less than the actual total aldicarb (and oxidative metabolites) present in the victim's body at the time of death.

Lee and Ransdell (1984) concluded that, although the direct cause of death of the victim was massive chest trauma, the toxicological analyses and the circumstances surrounding the accident indicated that aldicarb intoxication was a contributing factor. The victim was calculated to have nearly

TABLE VI-1

Residues of Aldicarb and Its Metabolites in Tissues of an Exposed Farmworker[a,b]

Tissue	Aldicarb (ppm)	Aldicarb Sulfoxide (ppm)	Aldicarb Sulfone (ppm)	Aldicarb Derivatives Total (ppm)
Blood	MDL[c]	0.108	0.374	0.482
Liver	0.013	0.058	0.116	0.187
Kidney	Trace[d]	0.261	0.422	0.683
Skin (hand)	0.492	0.157	0.174	0.823
Skin (abdomen)	0.005	0.015	Trace[e]	0.020
Skin (thigh)	0.168	0.126	0.083	0.377

[a] Source: Adapted from Lee and Ransdell, 1984

[b] No explanation provided for differences in reported minimal detectable levels

[c] Minimal detectable level = 0.028 ppm

[d] Less than 0.002 ppm

[e] Minimal detectable level = 0.024 ppm

3 times the level of blood and tissue aldicarb known to produce cholinergic symptoms in man [based upon the 0.1 mg/kg bw effect level in Haines (1971)], leading to the speculation that physical incapacitation may have occurred to the extent that he was unable to perform the necessary coordinated voluntary neuromuscular actions that might have prevented his death.

CDC (1979) and Goes et al. (1980) reported two incidences of suspected carbamate poisoning in Nebraska in 1977. In both instances, all individuals experiencing the symptoms of carbamate intoxication had just eaten hydroponically grown cucumbers purchased at the same market. (Hydroponic refers to the growing of plants in nutrient solutions, either with or without an inert medium to provide mechanical support.) In the first reported incident, nine residents of a Nebraska town suffered the onset of acute illness within 15 minutes to 2.25 hours following ingestion of hydroponic cucumbers produced in the same local greenhouse. The nine cases of illness, all experienced in a 2-week period, were characterized by the following symptoms: diarrhea, vomiting, excessive perspiration, blurred vision, abdominal pain, dyspnea, muscle fasciculation, nausea and, in some cases, headache and/or loss of function of arms and legs. One individual was reported to have convulsed. The victims, three males and six females, ranged in age from 7-80 years and experienced symptoms of the sudden illness for 4-12 hours. (There was one exception, an 80-year-old woman, who was hospitalized for 36-48 hours because of her age; no time was reported in her case for the cessation of symptoms.) Although none of the victims received specific medical treatment, all recovered quickly and completely. Analysis of medical records of those victims who sought medical help revealed that routine hematology and chemistry tests showed results within normal ranges. Cholinesterase levels were not determined, however. Although no specific chemical could be positively associated with the suspected poisonings, the rapidity of the onset of symptoms suggested chemical poisoning, and the nature of the symptoms suggested the agent was a cholinesterase inhibitor. Remaining portions of cucumbers obtained from the ill individuals were analyzed by thin layer chromatography. A carbamate was found to be present, but the exact species could not be determined.

In 1978, a second outbreak of similar illnesses was reported (CDC, 1979; Goes et al., 1980). This time five individuals became seriously ill after ingesting hydroponic cucumbers grown in the same greenhouse that had been involved in the 1977 poisonings. Onset of symptoms had occurred within 30-60 minutes of ingestion of the cucumbers. The victims, three males and two females ranging in age from 6-49 years, manifested symptoms of diarrhea, abdominal pains, excessive perspiration, nausea and vomiting, dyspnea, muscle fasciculation, headache and blurred vision. The duration of the illness ranged from 3.5-5.5 hours. As in the 1977 incident, the victims recovered completely and quickly without specific medical treatment. Cucumbers remaining on the shelf of the supermarket where the suspect cucumbers had been purchased were analyzed, along with various samples of materials from the greenhouse where they were grown. Aldicarb was identified in both samples of greenhouse materials and the two cucumbers analyzed. The two cucumbers were found to contain 6.6 and 10.7 ppm aldicarb, respectively. An additional two cucumbers were taken from an unopened shipment of 10 cucumbers in a warehouse and also analyzed. One of these was found to be uncontaminated, but the other contained 9.9 ppm aldicarb. Further, 1.8 ppm of this insecticide was identified in the water-nutrient solution that nourished the cucumber plants and another 0.6 ppm in a gravel sample taken from the cucumber bed. Although the eaten cucumbers obviously could not be assayed, the identified aldicarb in other cucumbers grown in the same greenhouse provides sufficient evidence to suggest that aldicarb was the etiologic agent of the reported 1977 and 1978 illnesses.

In a human study conducted by Haines (1971), three groups of four adult male human subjects were administered single oral doses of aldicarb (analytical grade, 99.2% pure) in water solutions corresponding to 0.1, 0.05 or 0.025 mg insecticide/kg bw. All subjects were determined to be in good health by the physicians supervising the experiment, and none had been exposed to aldicarb or other known anticholinesterase for at least 1 week prior to this study. Blood cholinesterase levels were monitored both before and after dosing, and symptoms resulting from the treatment were observed by the physicians. Blood samples were collected from all subjects 18 hours and 1 hour before ingestion of the aldicarb, and at 1, 2, 4 and 6 hours after dosing. Cholinesterase levels were determined by a radiometric procedure. Pre-treatment urine specimens were collected from each individual and used as untreated controls for the analyses of aldicarb and its metabolites obtained in post-treatment urine samples. The maximum 0.1 mg/kg bw dose was selected based upon the 0.1 mg/kg bw/day no-effect-level determined in the 2-year rat feeding study of Weil and Carpenter (1965). The other dosages selected for this experiment were one-half and one-fourth of the rat NOEL. Since the cholinesterase inhibition of aldicarb is rapidly reversed, preparation of blood sample slides was completed within 3 minutes of blood extraction. Once drying of the slides was completed, reversal of cholinesterase inhibition would not be expected to occur. The fraction of retained substrate was calculated from mean counts of sample and reference slides. Results of the blood and urine analyses are shown in Tables VI-2 and VI-3, respectively. Subjects receiving the 0.1 mg/kg dose manifested a variety of cholinergic symptoms including malaise, weakness in arms and legs, pupils contracted and nonreactive to light, epigastric cramping pain, sweating of hands and forehead, air hunger, frequent yawning, salivation, slurred speech, nausea and vomiting. The aldicarb-induced cholinesterase depression was reported to be rapidly reversible, and by 6 hours after administration, all symptoms had disappeared and the subjects were reported to feel normal again. The author noted that the observed reduction in cholinesterase activity appeared to be out of proportion to the nature of the symptoms, with two of the subjects receiving the 0.1 mg/kg dose having values as low as 25% (31% if 1-hour pre-dosing values are used) of their pre-exposure level. It was concluded that the radiometric analysis, which gives an average value for red cell and plasma cholinesterase, may yield a different interpretation than the usual analytical procedures that measure true acetylcholinesterase from the red cell. Further, statistical analysis of these data suggests a dose-related effect when the maximum pre-dose control value is considered, leading to the assumption that at lower levels of ingestion (0.002-0.004 mg/kg), a significant depression of erythrocyte cholinesterase would probably not occur.

TABLE VI-2

Effects on Symptomatology and Whole Blood Cholinesterase Following Ingestion of Aldicarb by Human Volunteers[a]

Subject No.	Amount Aldicarb Ingested		Blood Cholinesterase Levels[b]						Development of Symptoms
			Pre-Dose		Post-Dose				
	mg	mg/kg	18 hours	1 hour	1 hour	2 hours	4 hours	6 hours	
1	9.5	0.1	167	85[c]	58	68	107	123	yes[d]
2	8.7	0.1	149	112	69	45	83	119	yes[d]
3	8.3	0.1	218	185	57	47	84	120	yes[d]
4	6.5	0.1	176	175	55	35	120	149	yes[d]
5	4.9	0.05	129	191	77	93	139	152	no
6	4.4	0.05	171	159	64	62	136	134	pos.[e]
7	3.9	0.05	168	155	50	97	142	152	no
8	3.6	0.05	210	171	100	81	156	172	no
9	2.3	0.025	194	225	122	131	168	205	no
10	2.1	0.025	163	191	82	85	140	146	no
11	2.0	0.025	--	147	74	100	154	135	no
12	2.2	0.025	--	143	94	100	132	140	no

[a] Modified from Haines, 1971

[b] Observed hydrolysis rate of acetylcholine (µm/hr/mℓ)

[c] No explanation for the magnitude of this pre-treatment drop in cholinesterase was given.

[d] Present in first 2 hours after ingestion; none were visible after 4 hours

[e] Possible symptom in first hour; none thereafter

TABLE VI-3

Concentration of Total Toxic Carbamates in Urine Sampled at 1, 2, 4, 6 and 8 Hours After Ingestion of Known Amounts of Aldicarb*

Subject No.	Amount of Aldicarb Ingested (mg)	Urine Sample, Time After Ingestion (hours)	Weight of Urine Sample (grams)	Concentration of Total Toxic Carbamates (ppm)	Total Toxic Carbamates Excreted in Sample (μg)	Percent of Dose Excreted in Urine (8 hours)
1	9.5	1.1	682	0.18	123	8.4
		2.1	339	0.50	170	
		4.0	83	2.7	224	
		6.0	117	1.5	176	
		8.3	100	1.1	110	
2	8.7	1.0	85	0.79	75	9.5
		2.0	75	2.3	173	
		4.2	525	0.41	215	
		6.0	514	0.40	206	
		8.0	484	0.32	155	
3	8.3	1.0	348	0.20	70	8.0
		2.0	76	1.3	99	
		3.5	85	1.8	153	
		6.1	175	1.3	227	
		7.7	830	0.14	116	
4	6.5	1.1	213	0.35	75	7.1
		2.0	361	0.30	108	
		3.4	313	0.33	103	
		5.9	465	0.26	121	
		8.2	404	0.13	53	

TABLE VI-3 (cont.)

Subject No.	Amount of Aldicarb Ingested (mg)	Urine Sample, Time After Ingestion (hours)	Weight of Urine Sample (grams)	Concentration of Total Toxic Carbamates (ppm)	Total Toxic Carbamates Excreted in Sample (µg)	Percent of Dose Excreted in Urine (8 hours)
5	4.9	0.9	173	0.33	57	10.7
		2.0	202	0.47	95	
		4.0	833	0.29	242	
		6.4	298	0.32	95	
		8.2	455	0.08	36	
6	4.4	1.0	407	0.16	65	5.4
		2.0	414	0.18	75	
		4.1	75	0.27	20	
		6.1	275	0.19	52	
		7.9	203	0.13	26	
7	3.9	1.0	491	0.12	59	5.8
		2.0	512	0.16	82	
		4.1	90	0.33	30	
		6.0	146	0.25	36	
		8.0	255	0.08	20	
8	3.6	1.0	79	0.39	31	7.4
		2.0	92	0.69	64	
		4.3	308	0.26	80	
		5.9	491	0.17	49	
		7.9	478	0.09	43	
9	2.3	1.0	431	0.11	48	6.3
		2.0	418	0.07	29	
		4.0	314	0.12	38	
		6.1	156	0.11	17	
		7.8	326	0.04	13	

TABLE VI-3 (cont.)

Subject No.	Amount of Aldicarb Ingested (mg)	Urine Sample, Time After Ingestion (hours)	Weight of Urine Sample (grams)	Concentration of Total Toxic Carbamates (ppm)	Total Toxic Carbamates Excreted in Sample (µg)	Percent of Dose Excreted in Urine (8 hours)
10	2.1	0.9	232	0.18	42	8.9
		1.9	103	0.35	36	
		3.8	546	0.10	55	
		6.2	212	0.18	38	
		7.8	485	0.03	15	
11	2.0	0.8	542	0.06	33	9.1
		2.0	277	0.17	47	
		3.8	350	0.15	52	
		6.2	152	0.24	36	
		7.8	215	0.07	15	
12	2.2	0.9	63	0.54	34	10.4
		2.0	54	0.99	54	
		3.8	353	0.19	67	
		6.1	289	0.18	52	
		7.8	169	0.13	22	

*Modified from Haines, 1971

Sexton (1966) (cited in U.S. EPA, 1975) reported a case history of aldicarb poisoning experienced in a manufacturing plant. The victim of the poisoning was a foreman who ran a mechanical bagging machine for 1 day. Symptoms experienced included nausea, dizziness, depression, weakness, tightness of chest muscles, and decrease in plasma and RBC cholinesterase activity. The duration of symptoms was somewhat longer than 6 hours (exact duration unspecified), and the subject returned to work the following day without symptoms.

Epidemiological Studies

Following the detection of aldicarb in well water samples in Suffolk County, New York, Varma et al. (1983) conducted a mail survey of families whose wells had been tested for aldicarb. Information requested included family composition, length of residency, and farming-related questions such as farm size/acreage, number of full-time farmworkers and professional use of agricultural chemicals. Prospective respondents were requested to report every family member who had experienced any of a list of 20 general health problems, and women of reproductive age were to report the outcome of all pregnancies as well as the health of their children. A list of 25 randomly arranged neurological symptoms was also included for the respondent's identification of family members who had experienced any of them. The questionnaires were also mailed to additional addressees in that farm region; however, no attempt was made to determine whether the wells at these latter addresses had been tested for aldicarb. A total of 223 households known to have aldicarb water levels >7 ppb were divided into four groups of approximately equal size to study dose-related trends.

The response rate to the 1500+ questionnaires mailed was only ~20%. For a number of reasons, only households with aldicarb water concentrations ≥8 ppb were used for analysis of the results. Varma et al. (1983) reported that the self-reported health problems suggested an association between certain neurologic symptoms/syndromes and the concentration of aldicarb in the drinking water. The rate of spontaneous abortions (Table VI-4) was high among women consuming water with the highest aldicarb concentrations; however, it should be noted that the same group also had a high incidence of spontaneous abortions in the 7 years prior to the use of aldicarb in that farming region. A dose-related trend in the spontaneous abortion rates was observed for the 1975-1981 period; however, the abortion rates of 10 and 22.4% for the two study periods were not significantly different. The authors stated that selection and reporting bias could have influenced these findings, and that distortion at a survey response level as low as 20% could be a serious problem.

Varma et al. (1983) concluded that the findings of that study provided no conclusive evidence for the following reasons: 1) the data obtained was based upon information provided by residents and not from medical records; 2) there was a lack of gynecological histories and data from all pregnant women; 3) the response rate to the questionnaires mailed was very low; 4) the contamination level used in the analysis was based in most instances on a single water sample and, therefore, might not be indicative of a long-term contamination level; and 5) the possible presence of other synthetic chemicals used on the soil could not be overruled.

TABLE VI-4

Reported Pregnancies and Spontaneous Abortions Among Respondents to Suffolk County Mail Survey[a]

	Aldicarb Concentration Ranges (ppb)				
	8-15	16-35	36-65	66+	Totals/ Averages
Period: 1968-1974[b]					
Women responding	31	41	36	32	140
Women reporting pregnancies	4	8	7	6	25
Total pregnancies reported[c]	6	11	14	9	40
Spontaneous abortions[d]	1	0	1	2	4
Percent spontaneous abortions	16.7	0.0	7.1	22.2	10.0
Period: 1975-1981[e]					
Women responding	32	46	33	29	140
Women reporting pregnancies	9	10	9	7	35
Total pregnancies reported[c]	17	19	18	13	67
Spontaneous abortions[f]	1	6[g]	2	6[h]	15
Percent spontaneous abortions	5.9	31.6	11.1	46.2	22.4

[a] Source: Modifed from Varma et al., 1983

[b] Period prior to possible aldicarb exposure; concentration ranges merely denote geographic locations for comparison with 1975-1981 survey data.

[c] Includes multiple pregnancies by the same individual

[d] Trend spontaneous abortions, 1968-1974; $Z = 0.742$, $p>0.22$

[e] Period of possible aldicarb exposure

[f] Trend spontaneous abortions, 1975-1981; $Z = 1.912$, $p<0.028$

[g] One woman had two spontaneous abortions (also one normal delivery in each of the 1968-1974 and 1975-1981 time periods)

[h] One woman had two spontaneous abortions in this period; one woman had one each in the 1968-1974 and 1975-1981 periods (both also had normal pregnancies).

High Risk Subpopulations

Other than individuals involved in the manufacture, handling and use/application of aldicarb, there is no fully conclusive evidence of other groups being particularly at risk to the toxic effects of this insecticide. However, pregnant women, the very aged, and angina patients might exhibit particular sensitivity to its effects. A somewhat more detailed discussion of this area is included in Chapter VIII of this document.

Summary

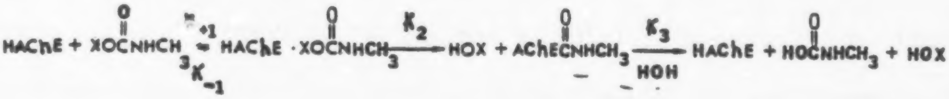
The symptoms reported for accidental or occupational poisoning (Sexton, 1966; CDC, 1979; Goes et al., 1980;) and controlled aldicarb human exposure (Haines, 1971) have all been cholinergic in nature and have all spontaneously subsided, generally within a 6-hour period. The nature and/or severity of some of the symptoms, however, such as skeletal muscle weakness, epigastric cramping pain, excessive sweating, nausea, vomiting and nonreactive contracted pupils in the controlled study and dizziness, dyspnea, diarrhea, blurred vision and muscle fasiculation or convulsions in the accidental poisoning cases, can result in health or life-threatening situations in certain occupational settings or in everyday activities such as driving an automobile.

VII. MECHANISMS OF TOXICITY

The primary mode of aldicarb toxicity is cholinesterase inhibition. Although it is commonly accepted that carbamate insecticides interfere with the ability of acetylcholinesterase (AChE) to break down the chemical transmitter acetylcholine (ACh) at synaptic and myoneural junctions, the precise biochemical mechanism for this interaction has yet to be clearly elucidated. It is known, however, that the same mechanism of action is evident in both target and nontarget organisms (Kuhr and Dorough, 1976). Aldicarb and other carbamate insecticides further cause depression of other cholinesterases ("pseudocholinesterases") in the red blood cells and plasma of humans and other vertebrate species (Carpenter and Smyth, 1965; Weil and Carpenter, 1968a,b,c, 1969; Dorough et al., 1970; Nycum and Carpenter, 1970; Shlinke, 1970; Weil and Carpenter, 1970; Mirro et al., 1982), but the degree of inhibition necessary to produce adverse effects in exposed subjects/animals is speculative and the subject of current concern. Various cholinesterases have also been identified in the brain, liver, pancreas, intestine, heart and skeletal muscle of mammals, and may be distinguished from one another, and from AChE ("true cholinesterases") by substrate and inhibitor specificity (Kuhr and Dorough, 1976; Cambon et al., 1980).

Without going into a lengthy discussion of the morphology and function of the mammalian neuromuscular system, the transmission of electrical impulses between nerves and at myoneural junctions generally occurs through the release of chemical transmitters which bind with specific receptors on the postsynaptic terminal or motor end plate, respectively. As the chemical transmitter, acetylcholine in certain nerve synapses and at neuromuscular junctions, binds to the receptor sites, an esterase (AChE) rapidly hydrolyzes the ACh into acetyl and choline fractions so that the stimulated nerves or muscles are not continually excited. Essentially, aldicarb and other cholinesterase inhibitors in some way prevent the breakdown of ACh and the subsequent return to a more normal or resting state for the nerve and/or muscle cells.

As opposed to the long-lasting cholinesterase inhibition associated with organophosphate pesticides, the carbamylation reactions involving the carbamates produce toxicity of a considerably shorter and more transient duration (Doull et al., 1980). Kuhr and Dorough (1976) suggest a formula for the reaction of N-methyl carbamate insecticides with acetylcholinesterase:



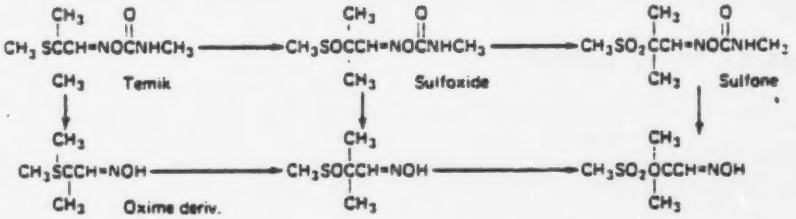
$$\text{HAChE} + \text{XO}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{NHCH}_3 \underset{K_{-1}}{\overset{K_{+1}}{\rightleftharpoons}} \text{HAChE}\cdot\text{XO}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{NHCH}_3 \xrightarrow{K_2} \text{HOX} + \text{AChE}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{NHCH}_3 \xrightarrow[\text{HOH}]{K_3} \text{HAChE} + \text{HO}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{NHCH}_3 + \text{HOX}$$

In this process, the enzyme HAChE reacts with the pesticide to form an intermediate complex which may: 1) dissociate to enzyme and carbamate, or 2) decompose into a stable carbamylated enzyme plus a leaving group, which is the parent phenol, napthol or oxime (as in the case of aldicarb). The carbamylated enzyme is then hydrolyzed to generate free enzyme and methyl carbamic acid. It should be noted that this reaction sequence does not result in the destruction of AChE, but rather the hydrolysis of the insecticide molecule itself.

During a normal nerve impulse, the AChE cleaves the ACh molecule. When a carbamate insecticide such as aldicarb enters the synapse, however, it competes with ACh for the active site on the enzyme. Since the decomposition to a carbamylated enzyme and leaving group, as well as the hydrolysis of the carbamylated enzyme, occur "thousands of times" slower when the active site is occupied with the carbamate than with ACh, the enzyme is essentially and effectively inhibited and the normal cleavage of the ACh molecule by its esterase would be precluded. The greater the quantity of carbamate present, the greater the enzyme inhibition and concomitant reduction/slowing of ACh excitatory activity.

Reversal of this process may occur in two ways: 1) through dissociation of the pesticide-enzyme complex, and 2) a decarbamylation reaction, the half-life of which has been estimated to be ~30-40 minutes (O'Brien, 1967; Reiner and Aldridge, 1967). By these mechanisms, if insecticide exposure were not continual, recovery from anti-AChE activity would begin within a few minutes of carbamylation and be complete (and the associated symptoms dissipated) within a matter of hours. This has been observed to be the case in human exposures (Weil and Carpenter, 1970; CDC, 1979; Goes et al., 1980).

The *in vivo* metabolism of aldicarb (discussed in Chapter III) transforms the parent insecticide without activation into the more potent sulfoxide and sulfone cholinesterase inhibiting forms, as diagramatically shown below.



Signs and symptoms of aldicarb intoxication are typically cholinergic (also previously discussed) and may be ameliorated by the administration of atropine sulfate (Doull et al., 1980).

Further illumination of the mechanism of sensitivity to aldicarb was provided by Cambon et al. (1980). In a study described in Chapter V of this document, a significant inhibition of maternal and fetal cerebral AChE was noted following exposure of the dams. This study, described the existence of three distinct isoenzymes which were involved, and reported that the treatment produced a significant lowering in the dams of the least mobile of the three (isoenzyme 1) and a decrease of isoenzymes 1 and 2 in the fetuses. Cambon and his co-workers suggested that the greater inhibition observed in fetal brain AChE activity in a previous study (Cambon et al., 1979) might be due to the binding of the inhibitors for two of the isoenzymes in the fetuses as opposed to only the first isoenzyme in the mothers at the same dosage level, thereby indicating a greater affinity of the carbamate derivatives, such as aldicarb, for each respective fetal and maternal isoenzyme.

Aldicarb thus far has been found to exhibit no carcinogenic, mutagenic or teratogenic activity (see Chapter V), but the potential for the in vivo transformation to the nitroso derivative (which is carinogenic) has been suggested as a likely possibility.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the noncarcinogenic and carcinogenic effects. In the quantification of noncarcinogenic effects, an acceptable daily intake (ADI) is calculated. An adjusted acceptable daily intake (AADI) and health advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day) (body weight in kg)}}{\text{Uncertainty (Safety) Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking water volume in } \ell\text{/day}} = \text{mg/}\ell$$

where: NOAEL = no-observed-adverse-effect level

LOAEL = lowest-observed-adverse-effect level

Body weight = 70 kg for adult or 10 kg for child

Drinking water volume = 2 ℓ/day for adults or 1 ℓ/day for children

Uncertainty/Safety Factor = 10, 100 or 1000

Utilizing these relationships, the following drinking water concentrations are developed for noncarcinogenic effects:

1. A 1-day HA for 10 kg child
2. A 1-day HA for 70 kg adult
3. A 10-day HA for 10 kg child
4. A 10-day HA for 70 kg adult
5. A lifetime AADI for a 70 kg adult

The distinctions made between the HA calculations (items 1-4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1-2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spill or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon noncarcinogenic effects.

A NOAEL or LOAEL may be determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method for extrapolating from animals to humans. The possibility also must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivities to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS, 1977) are typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data are available and supported by acute or chronic toxicity data in other species.
- An uncertainty factor of 100 is used when good acute or chronic toxicity data identifying a NOEL/NOAEL are available for one or more species, but human data are not available.
- An uncertainty factor of 1000 is used when limited or incomplete acute or chronic toxicity data are available or when the acute or chronic toxicity data identifying only a LOAEL (but not NOEL/NOAEL) for one or more species are available.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated into the NAS/ODW guidelines for selection of an uncertainty factor, but which must be considered, include the following: 1) the quality of the toxicology data, 2) the significance of the adverse effect, and 3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (there is no evidence upon which to classify aldicarb as a carcinogen following oral exposure), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical by drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans, these data must be converted to an equivalent human dose. This conversion includes correction for noncontinuous animal feeding, nonlifetime studies and difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 ℓ of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer for choosing among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk levels, several other areas of uncertainty exist, such as 1) incomplete knowledge concerning the health effects of contaminants in drinking water, 2) the impact of test animal age, sex and species and impact of the target organ systems examined on the observed toxicity, and 3) the actual rate of exposure of internal targets (effective dose) in test animals or humans. Dose-response data are usually only available for high levels of exposure, and not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Aldicarb is an oxime carbamate, soil-applied systemic insecticide used against certain insects, mites and nematodes. A review of the data presented in previous chapters of this document reveals that the inhibitory effect exhibited on plasma, erythrocyte and brain cholinesterase constitutes the primary toxicologic effect of aldicarb and its sulfoxide and sulfone metabolites. This inhibition has been further demonstrated to be transient in nature (barring continuous, high-level exposure) due to the spontaneous recovery of the inhibited enzyme.

Noncarcinogenic Effects

Although a substantive number of studies of the toxic effects of aldicarb exposure have been discussed in Chapters V and VI, the focus here shall be directed toward those experiments that are more widely accepted as providing a defensible basis for (or application to) risk assessment, studies utilizing drinking water as a source of exposure, or controlled human experimentation. Therefore, the discussion and development of HA, ADI and AADI levels will rely upon the Weil and Carpenter (1968b,c), Haines (1971) and Mirro et al. (1982) studies. A list of NOELs from these and other studies is included in Table VIII-1 for comparative purposes.

In the Weil and Carpenter (1968b,c) studies, groups of rats were administered oral doses of aldicarb sulfoxide at levels of 0.125, 0.25, 0.5 or 1.0 mg/kg bw or aldicarb sulfone at levels of 0.2, 0.6, 1.8, 5.4 or 16.2 mg/kg bw for periods of up to 6 months. Animals were sacrificed after 3 and 6 months of treatment and examined for tissue effects and plasma, erythrocyte and brain cholinesterase activity. The results of both studies revealed a substantial reduction of cholinesterase activity at the three highest dosage levels of each test compound when measured immediately upon cessation of feeding. Plasma cholinesterase was found to undergo the greatest reduction, and brain cholinesterase the least. Although no mortality or tissue effects (gross or microscopic) were noted, some level of growth retardation was reported at the highest treatment dosages. When rats receiving similar dosages of the aldicarb sulfoxide and sulfone compounds for 3 months were placed on a control diet for a 1-day recovery period at the end of the treatment, a rapid recovery from the cholinesterase inhibition was reported for all but the highest dosages of sulfoxide and sulfone.

TABLE VIII-I

Observed NOEL Values for Aldicarb and Its Metabolites in Various Species[a]

Study	End-Point	NOEL (mg/kg/day)	Reference
Rat, 2-year, aldicarb, aldicarb sulfone (sulfoxide: sulfone mixture)	somatic effects	0.3 (0.6)	Weil and Carpenter, 1972
Rat, 2-year, aldicarb	various	0.1[b]	Weil and Carpenter, 1965
Rat, 6-month, aldicarb sulfoxide	cholinesterase inhibition	0.125	Weil and Carpenter, 1968b
Rat, 4-week aldicarb sulfoxide:sulfone (1:1 mixture)	cholinesterase inhibition	0.12	Mirro et al., 1982
Dog, 2-year, aldicarb	various	0.1[b]	Weil and Carpenter, 1966
Dog, 3-month, aldicarb sulfoxide	various	0.25	Weil and Carpenter, 1968b
Rat, 3-generation, aldicarb	reproduction	0.7[b]	Weil and Carpenter, 1974a
Rat, teratology aldicarb	teratogenicity	1.0[b]	Weil and Carpenter, 1966
Rat, 3-month, aldicarb	dominant lethal	0.7[b]	Weil and Carpenter, 1974a
Rat, 2-year, aldicarb	oncogenicity	0.3[b] (6 ppm in diet)	NCI, 1979
Mouse, 18-month, aldicarb	oncogenicity	0.7[b]	Weil and Carpenter, 1974b
Hen, 30 days, aldicarb	delayed neurotoxicity	4.5[b]	Johnson and Carpenter, 1966
Human, single dose aldicarb	cholinesterase inhibition	0.025-0.05	Haines (1971)

[a] Modified from Wilkinson et al., 1983

[b] Highest level tested

Based upon these studies, a NOEL of 0.125 mg/kg bw was determined for the more toxic sulfoxide in rats.

In a 4-week study in which young Wistar rats were administered a 1:1 mixture of aldicarb sulfoxide and aldicarb sulfone in drinking water at concentrations of 0, 0.075, 0.3, 1.2, 4.8 or 19.2 ppm, Mirro et al. (1982) assessed the level of cholinesterase inhibition resulting from the treatment. Individual dosage levels ranged from 0 for controls to 1.67 mg/kg/day for males and 1.94 mg/kg/day for females at the 19.2 ppm concentration. Plasma and RBC cholinesterase was examined in 8-, 15- and 29-day blood samples, and brain cholinesterase was determined upon sacrifice after 29 days. A 64-77% reduction in plasma cholinesterase was observed in all animals receiving the 19.2 ppm dosage, while the 4.8 ppm treatment concentration was reported to cause a statistically significant (28% mean) decrease in plasma cholinesterase in male rats only after 8 days of treatment. Erythrocyte cholinesterase activity underwent a 48-63% reduction in animals receiving the highest dosage level, and the reduction was noted at all sampling periods. The lowest sulfoxide:sulfone concentration producing a significant decrease (24% mean; $0.05>p>0.01$) in RBC cholinesterase was 4.8 ppm, and this reduction was reported to have occurred only in males after 29 days from onset of treatment. A statistically significant reduction (10%) in brain cholinesterase was reported only for females at day 29 following treatment at the highest dosage level. Body weight changes and water consumption were also observed to be decreased at the highest dose in rats of both sexes at 7, 14, 21 and 29 days; food consumption was reduced in males during the same time and in females on day 7, only. Based upon the reported reductions in plasma and RBC cholinesterase activities, a NOEL of 1-2 ppm

(0.12 mg/kg bw) can be determined. This NOEL warrants special consideration, however, since it is based upon the effects of a 1:1 mixture of aldicarb sulfoxide and aldicarb sulfone. Since the sulfone has been demonstrated to be a notably less potent inhibitor of cholinesterase activity (Weil, 1975), the NOEL might logically be expected to be somewhat lower if the treatment had consisted of the sulfoxide alone.

When all available data on the toxicity of aldicarb are considered, the most appropriate basis for the determination of HAs and an ADI would be cholinesterase inhibition. The Safe Drinking Water Committee of the National Academy of Sciences (NAS, 1977) recommended an ADI for aldicarb in drinking water of 1 μg/kg. This value was derived by applying a 100-fold safety (uncertainty) factor to the 0.1 mg/kg/day NOELs determined in 2-year rat (Weil and Carpenter, 1965) and dog (Weil and Carpenter, 1966) feeding studies. The joint FAO/WHO Expert Committee on Pesticide Residues (FAO/WHO, 1980) similarly recommended an ADI for humans of 1 μg/kg based upon the 0.125 mg/kg bw/day 6-month rat feeding study of Weil and Carpenter (1968a) and utilizing a safety factor of 100. However, this same committee revised the ADI upward to 5 μg/kg bw/day in 1982. A 1979 FIFRA Scientific Advisory Panel, convened at the request of the U.S. EPA Office of Pesticide Programs, supported the ADI of 1 μg/kg for humans previously recommended by the NAS (1977) and the FAO/WHO (1980), confirming the appropriateness of the 0.125 mg/kg/day NOEL and the 100-fold safety factor for ADI derivation (U.S. EPA, 1980a). The U.S. EPA Office of Pesticide Programs originally determined an ADI value for aldicarb and its sulfoxide metabolite of 3 μg/kg based upon the 0.3 mg/kg bw/day NOEL from the 2-year rat feeding study of Weil and Carpenter (1972) and a safety factor of 100. However, in the

Federal Register (1981, 1982) a new basis for the 3 µg/kg human ADI was announced, namely the acceptance of the 0.125 mg/kg bw/day NOEL from the 6-month aldicarb sulfoxide rat feeding study of Weil and Carpenter (1968b) and a safety factor of ~40.

A current and thorough re-evaluation of the literature available to date confirms the 0.125 mg/kg/day NOEL from the Weil and Carpenter (1968b) study as the most appropriate NOEL for the determination of a human ADI. However, the Mirro et al. (1982) study of drinking water exposure provides not only a supportive NOEL of 0.12 mg/kg/day, but further suggest a return to a safety factor of 100. The reasoning behind this statement is 4-fold:

1. It is in complete consonance with the guidelines for a 100-fold safety factor adopted by the NAS (1977): i.e., "A safety factor of 100 may be applied in cases where data on prolonged human studies are not available or are scanty (e.g., only acute exposures), where valid results on long-term animal feeding studies are available with several species, and where there is no evidence of carcinogenicity."
2. The 0.12 mg/kg bw/day NOEL of the Mirro et al. (1982) study is based upon a 1:1 ratio mixture of aldicarb sulfoxide and the less toxic aldicarb sulfone.
3. The 0.125 mg/kg/day level is reasonably supported by the 0.1 mg/kg/day NOEL of the 2-year rat and dog feeding studies of Weil and Carpenter (1965, 1966), although 0.1 mg/kg/day was the highest dose tested in these experiments.
4. The Cambon et al. (1979) study indicated a sensitivity of fetal rats to cholinesterase inhibition far greater than that observed in adults. This study revealed AChE inhibition in the fetal blood, brain and liver just 1 hour following a dosage 1000 times lower than the LD_{50} for aldicarb in the adult. Thus, a safety/uncertainty factor of 100 should be employed to assure a necessary degree of protection to this potentially sensitive subgroup.

Although the Haines (1971) study provides the only data available involving controlled human experimentation, the single-dose treatment employed is not sufficiently comparable to the intermittent exposure associated with intake of a comparable level of toxicant over a prolonged period of time (i.e., 24-hour day or 16-hour waking day). Further, application of a 10-fold safety factor to the 0.025 mg/kg bw dosage which the author states resulted in "transient mild cholinesterase inhibition insufficient to cause symptoms" in humans would result in an ADI of 2.5 µg/kg bw, but might not provide adequate protection for any sensitive subpopulations. Nevertheless, the single-dose method of administration is inappropriate for ADI derivation for humans.

Quantification of Noncarcinogenic Effects

Given the nature of the primary toxicity of aldicarb and its metabolites (rapidly reversible cholinesterase inhibition), it is apparent that the same NOEL can be used as the basis for the derivation of acceptable levels over virtually any duration of exposure. As described above, a NOEL of 0.125 mg/kg bw/day can be determined from the Weil and Carpenter (1968b) and Mirro, et al. (1982) studies. From this NOEL, HA and ADI/AADI values can be determined.

1-day HA.

For the 10 kg child:

$$\frac{0.125 \text{ mg/kg/day} \times 10 \text{ kg}}{100 \times 1 \text{ ℓ}} = 0.012 \text{ mg/ℓ}$$

where:

0.125 mg/kg/day = NOEL, based upon lack of significant decreases in cholinesterase activity in rats

10 kg = weight of protected individual

100 = uncertainty factor, appropriate for use with animal NOEL

1 ℓ = 1 liter, assumed volume of water consumed/day by 10 kg child

For the 70 kg adult:

$$\frac{0.125\ \text{mg/kg/day} \times 70\ \text{kg}}{100 \times 2\ \ell} = 0.042\ \text{mg}/\ell$$

where:

70 kg = weight of protected individual

2 ℓ = 2 liters, assumed volume of water consumed/day by 70 kg adult

(Other factors as described above for 10 kg child)

10-day HA. Since aldicarb is metabolized and excreted rapidly (>90% in urine alone in a 24-hour period following a single dose), the 1- and 10-day HA values would not be expected to differ to a significant or notable extent. Therefore, it is proposed that the 10-day HAs be the same as the 1-day HAs.

ADI/AADI. As stated above, the ADI for the 70 kg adult can be determined from data yielding a NOEL of 0.125 mg/kg/day. Using these data, the ADI would be derived as follows:

$$\text{ADI} = \frac{0.125\ \text{mg/kg bw/day}}{100} = 1.2\ \mu\text{g/kg bw/day (or 84}\ \mu\text{g/day for a 70 kg adult)}$$

The AADI for the 70 kg adult would be derived as follows:

$$\text{AADI} = \frac{\text{ADI}}{2\ \ell} = \frac{84\ \mu g/\text{day}}{2\ \ell} = 42\ \mu g/\ell$$

Conventional toxicological procedures would lead one to develop an AADI from an ADI for the 70 kg adult in the manner described above. However, in the case of aldicarb, this may be inappropriate, since an acceptable level would be virtually identical for all durations of exposure. While the AADI shown above (42 μg/ℓ) might be considered sufficiently protective for the 70 kg adult over all durations of exposure, it may not be sufficiently protective for the 10 kg child, a significant subset of the population, over less-than-lifetime durations of exposure. Therefore, consideration should be given to the option of establishing the AADI for aldicarb at a level determined to be protective of the 10 kg child, namely 12 μg/ℓ.

The AADI(s) proposed above (and summarized in Table VIII-2) reflect the assumption that 100% of the exposure to aldicarb is via the drinking water. Since this chemical is used on food crops, the potential exists for dietary exposure also. When the percentage contribution from the diet is determined, the AADI(s) should be adjusted to accomodate this factor.

Carcinogenic Effects

An NCI (1979) bioassay of aldicarb in which rats and mice were fed either 2 or 6 ppm in the diet for 103 weeks revealed no tumors that could be attributed solely to aldicarb administration. It was concluded that, under the conditions of the bioassay, technical grade (99+%) aldicarb was not carcinogenic for F344 rats or $B6C3F_1$ mice of either sex. A 2-year feeding study reported by Weil and Carpenter (1965) also produced no statistically

TABLE VIII-2

Summary of Quantification of Toxicological Effects

Situation	Drinking Water Concentration (mg/ℓ)[a] 10 kg child	Drinking Water Concentration (mg/ℓ)[a] 70 kg adult	Reference[b]
1-day HA	0.012	0.042	Weil and Carpenter, 1968b; Mirro et al., 1982
10-day HA	0.012	0.042	Weil and Carpenter, 1968b; Mirro et al., 1982
AADI		0.042 (0.012)	Weil and Carpenter, 1968b; Mirro et al., 1982
Estimated Excess Cancer Risk			
10^{-4}		NC[c]	
10^{-5}		NC	
10^{-6}		NC	

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[a] Assumes 100% contribution from drinking water; modifications necessary after determination of relative source contribution, particularly diet.

[b] Reference from which NOEL was identified and applied in calculating HAs/AADIs

[c] Not calculated; no indication of carcinogenic potential

significant increase in tumors over controls when rats were administered equivalent doses of 0.005, 0.025, 0.05 or 0.1 mg aldicarb/kg/day in the diet. Weil (1975) similarly reported no adverse effects in Greenacres Laboratory Controlled Flora rats fed 0.3 mg aldicarb/kg bw/day for 2 years. In the only skin-painting study available to date, Weil and Carpenter (1966) found aldicarb to be noncarcinogenic to male C3H/H3J mice under the conditions of the experiment.

Quantification of Carcinogenic Effects

Since aldicarb has been found to be noncarcinogenic under all conditions tested, quantification of carcinogenic risk for lifetime exposures through drinking water would be inappropriate.

Special Considerations

Synergistic Interactions. No positive evidence of potentiation of the effects of aldicarb during concomitant exposure to other pesticides could be located in the available literature. West and Carpenter (1966) found no evidence of potentiation when combinations of aldicarb and carbaryl on eight organophosphorous insecticides were administered to rats. A study of possible potentiation between aldicarb and carbofuran residues by the Hazard Evaluation Division of the U.S. EPA Office of Pesticide Programs (U.S. EPA 1980b) further concluded that the combined toxicological effect of mixtures of these two carbamates is additive and that no potentiation occurs. It should be noted, however, that the nitrosation of aldicarb has been demonstrated to result in DNA damage (Blevins et al., 1977) and transforming or tumorigenic activity (Quarles et al., 1979).

High-Risk Subpopulations. Individuals possessing a higher than normal risk of aldicarb poisoning include those involved in its manufacture, handling, processing, storing, mixing and field application. Recent studies by Cambon et al. (1979, 1980) with rats have indicated that fetuses might be particularly sensitive to the cholinesterase inhibition resulting from exposure of the mother to aldicarb. There is also some indication in the Goes et al. (1980) report on accidental aldicarb poisoning through ingestion of contaminated cucumbers that the very aged might also be more severely effected by exposure to this insecticide than would the general population. The symptoms of air hunger and dypsnea reported by Haines (1971) and Goes et al. (1980), respectively, for human exposure cases further suggest the potential for particular sensitivity in individuals suffering from angina pectoris, emphysema, or other chronic or acute respiratory disorders.

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